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(54) Title:	QUINAZOLINE DERIVATIVES		
(57) Abstract	<p>The invention relates to the use of compounds of formula (I), wherein: ring C is a 5-6-membered heterocyclic moiety; Z is -O-, -NH-, -S- or -CH₂-; R¹ is hydrogen, C₁₋₄alkyl, C₁₋₄alkoxymethyl, di(C₁₋₄alkoxy)methyl, C₁₋₄alkanoyl, trifluoromethyl, cyano, amino, C₂₋₅alkenyl, C₂₋₅alkynyl, carboxy, C₃₋₇cycloalkyl, C₃₋₇cycloalkyl C₁₋₃alkyl, or an optionally substituted group selected from phenyl, benzyl, phenylC₂₋₄alkyl and a 5-6-membered heterocyclic group; n is an integer from 0 to 5; m is an integer from 0 to 3; R² represents hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkylsulphanyl, -NR³R⁴ (wherein R³ and R⁴, which may be the same or different, each represents hydrogen or C₁₋₃alkyl), or R⁵X¹- (wherein X¹ represents a direct bond, -CH₂- or a heteroatom linker group and R⁵ is an alkyl, alkenyl or alkynyl chain optionally substituted by for example hydroxy, amino, nitro, alkyl, cycloalkyl, alkoxyalkyl, or an optionally substituted group selected from pyridone, phenyl and a heterocyclic ring, which alkyl, alkenyl or alkynyl chain may have a heteroatom linker group, or R⁵ is an optionally substituted group selected from pyridone, phenyl and a heterocyclic ring, and salts thereof, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals, processes for the preparation of such compounds, pharmaceutical compositions containing a compound of formula (I) or a pharmaceutically acceptable salt thereof as active ingredients and compounds of formula (I). The compounds of formula (I) and the pharmaceutically acceptable salts thereof inhibit the effects of VEGF, a property of value in the treatment of a number of disease states including cancer and rheumatoid arthritis.</p>		
	<p style="text-align: right;">(I)</p>		

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QUINAZOLINE DERIVATIVES

The present invention relates to quinazoline derivatives, processes for their preparation, pharmaceutical compositions containing them as active ingredient, methods for 5 the treatment of disease states associated with angiogenesis and/or increased vascular permeability, to their use as medicaments and to their use in the manufacture of medicaments for use in the production of antiangiogenic and/or vascular permeability reducing effects in warm-blooded animals such as humans.

Normal angiogenesis plays an important role in a variety of processes including 10 embryonic development, wound healing and several components of female reproductive function. Undesirable or pathological angiogenesis has been associated with disease states including diabetic retinopathy, psoriasis, cancer, rheumatoid arthritis, atheroma, Kaposi's sarcoma and haemangioma (Fan et al, 1995, Trends Pharmacol. Sci. 16: 57-66; Folkman, 1995, Nature Medicine 1: 27-31). Alteration of vascular permeability is thought to play a role 15 in both normal and pathological physiological processes (Cullinan-Bove et al, 1993, Endocrinology 133: 829-837; Senger et al, 1993, Cancer and Metastasis Reviews, 12: 303-324). Several polypeptides with in vitro endothelial cell growth promoting activity have been identified including, acidic and basic fibroblast growth factors (aFGF & bFGF) and vascular 20 endothelial growth factor (VEGF). By virtue of the restricted expression of its receptors, the growth factor activity of VEGF, in contrast to that of the FGFs, is relatively specific towards endothelial cells. Recent evidence indicates that VEGF is an important stimulator of both normal and pathological angiogenesis (Jakeman et al, 1993, Endocrinology, 133: 848-859; Kolch et al, 1995, Breast Cancer Research and Treatment, 36:139-155) and vascular 25 permeability (Connolly et al, 1989, J. Biol. Chem. 264: 20017-20024). Antagonism of VEGF action by sequestration of VEGF with antibody can result in inhibition of tumour growth (Kim et al, 1993, Nature 362: 841-844). Basic FGF (bFGF) is a potent stimulator of angiogenesis (e.g. Hayek et al, 1987, Biochem. Biophys. Res. Commun. 147: 876-880) and raised levels of FGFs have been found in the serum (Fujimoto et al, 1991, Biochem. Biophys. 30 Res. Commun. 180: 386-392) and urine (Nguyen et al, 1993, J. Natl. Cancer. Inst. 85: 241-242) of patients with cancer.

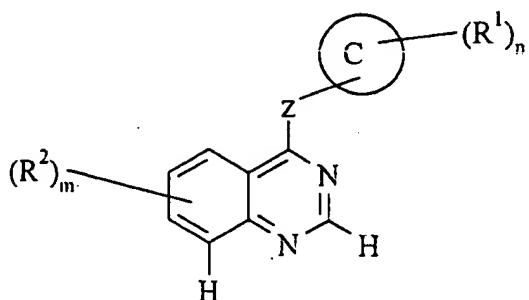
Receptor tyrosine kinases (RTKs) are important in the transmission of biochemical signals across the plasma membrane of cells. These transmembrane molecules

characteristically consist of an extracellular ligand-binding domain connected through a segment in the plasma membrane to an intracellular tyrosine kinase domain. Binding of ligand to the receptor results in stimulation of the receptor-associated tyrosine kinase activity which leads to phosphorylation of tyrosine residues on both the receptor and other 5 intracellular molecules. These changes in tyrosine phosphorylation initiate a signalling cascade leading to a variety of cellular responses. To date, at least nineteen distinct RTK subfamilies, defined by amino acid sequence homology, have been identified. One of these subfamilies is presently comprised by the fms-like tyrosine kinase receptor, Flt or Flt1, the kinase insert domain-containing receptor, KDR (also referred to as Flk-1), and another 10 fms-like tyrosine kinase receptor, Flt4. Two of these related RTKs, Flt and KDR, have been shown to bind VEGF with high affinity (De Vries et al, 1992, Science 255: 989-991; Terman et al, 1992, Biochem. Biophys. Res. Comm. 1992, 187: 1579-1586). Binding of VEGF to these receptors expressed in heterologous cells has been associated with changes in the tyrosine phosphorylation status of cellular proteins and calcium fluxes.

15 The present invention is based on the discovery of compounds that surprisingly inhibit the effects of VEGF, a property of value in the treatment of disease states associated with angiogenesis and/or increased vascular permeability such as cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, excessive scar 20 formation and adhesions, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation. Compounds of the present invention generally possess higher potency against VEGF receptor tyrosine kinase than against epidermal growth factor (EGF) receptor tyrosine kinase. Compounds of the invention which have been tested possess activity against VEGF receptor tyrosine kinase such that they may be used in an amount 25 sufficient to inhibit VEGF receptor tyrosine kinase whilst demonstrating no significant activity against EGF receptor tyrosine kinase. Compounds of the present invention generally possess higher potency against VEGF receptor tyrosine kinase than against FGF R1 receptor tyrosine kinase. Compounds of the invention which have been tested possess activity against VEGF receptor tyrosine kinase such that they may be used in an amount sufficient to inhibit 30 VEGF receptor tyrosine kinase whilst demonstrating no significant activity against FGF R1 receptor tyrosine kinase.

According to one aspect of the present invention there is provided the use of compounds of the formula I:

5



10

(I)

wherein:

ring C is a 5-6-membered heterocyclic moiety which may be saturated or unsaturated, which may be aromatic or non-aromatic, and which contains 1-3 heteroatoms selected independently

15 from O, N and S;

Z is -O-, -NH-, -S- or -CH₂-;

R¹ represents hydrogen, C₁₋₄alkyl, C₁₋₄alkoxymethyl, di(C₁₋₄alkoxy)methyl, C₁₋₄alkanoyl, trifluoromethyl, cyano, amino, C₂₋₅alkenyl, C₂₋₅alkynyl, a phenyl group, a benzyl group or a 5-6-membered heterocyclic group with 1-3 heteroatoms, selected independently

20 from O, S and N, which heterocyclic group may be aromatic or non-aromatic and may be saturated (linked via a ring carbon or nitrogen atom) or unsaturated (linked via a ring carbon atom), and which phenyl, benzyl or heterocyclic group may bear on one or more ring carbon atoms up to 5 substituents selected from hydroxy, halogeno, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkanoyloxy, trifluoromethyl, cyano, amino, nitro, C₂₋₄alkanoyl, C₁₋₄alkanoylamino, C₁₋₄alkoxycarbonyl, C₁₋₄alkylsulphonyl, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphinyl, C₁₋₄alkylsulphonyl carbamoyl, N-C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl, N,N-di(C₁₋₄alkyl)aminosulphonyl, C₁₋₄alkylsulphonyl amino, and a saturated heterocyclic group selected from morpholino, thiomorpholino, pyrrolidinyl, piperazinyl, piperidinyl imidazolidinyl and pyrazolidinyl, which saturated heterocyclic group may bear 1 or 2

25 substituents selected from oxo, hydroxy, halogeno, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkanoyloxy, trifluoromethyl, cyano, amino, nitro and C₁₋₄alkoxycarbonyl, and additionally substituents on the phenyl, benzyl or heterocyclic group may be selected from C₁₋₄alkylamino, C₁₋₄

₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄haloalkyl, C₁₋₄hydroxyalkoxy and carboxy; and
additionally R¹ may represent carboxy, C₃,cycloalkyl, C₃₋₇cycloalkylC₁₋₃alkyl, or phenylC₂₋₄alkyl wherein the phenyl moiety may bear up to 5 substituents selected from the list hereinbefore defined for a phenyl ring which is directly linked to ring C;

- 5 n is an integer from 0 to 5;
 m is an integer from 0 to 3;
 R² represents hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkylsulphanyl, -NR³R⁴ (wherein R³ and R⁴, which may be the same or different, each represents hydrogen or C₁₋₃alkyl), or R⁵X¹- (wherein X¹ represents a direct bond, -O-, -CH₂-, -OCO-, carbonyl, -S-, -SO-, -SO₂-, -NR⁶CO-, -CONR⁷-, -SO₂NR⁸-, -NR⁹SO₂- or -NR¹⁰- (wherein R⁶, R⁷, R⁸, R⁹ and R¹⁰ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl), and R⁵ is selected from one of the following seventeen groups:
 1) hydrogen or C₁₋₅alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro and amino, and additionally chloro and bromo;
 2) C₁₋₅alkylX²COR¹¹ (wherein X² represents -O- or -NR¹²- (in which R¹² represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹¹ represents C₁₋₃alkyl, -NR¹³R¹⁴ or -OR¹⁵ (wherein R¹³, R¹⁴ and R¹⁵ which may be the same or different each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl, or C₄₋₅alkyl));
 3) C₁₋₅alkylX³R¹⁶ (wherein X³ represents -O-, -S-, -SO-, -SO₂-, -OCO-, -NR¹⁷CO-, -CONR¹⁸-, -SO₂NR¹⁹-, -NR²⁰SO₂- or -NR²¹- (wherein R¹⁷, R¹⁸, R¹⁹, R²⁰ and R²¹ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹⁶ represents hydrogen, C₁₋₃alkyl, cyclopentyl, cyclohexyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C₁₋₃alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C₁₋₄alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl and C₁₋₄alkoxy, and additional possible substituents for the cyclic group are C₁₋₄cyanoalkyl and C₁₋₄alkoxycarbonyl);
 4) C₁₋₅alkylX⁴C₁₋₅alkylX⁵R²² (wherein X⁴ and X⁵ which may be the same or different are each -O-, -S-, -SO-, -SO₂-, -NR²³CO-, -CONR²⁴-, -SO₂NR²⁵-, -NR²⁶SO₂- or -NR²⁷- (wherein R²³, R²⁴, R²⁵, R²⁶ and R²⁷ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃

,alkoxyC₂₋₃alkyl) and R²² represents hydrogen or C₁₋₃alkyl, or R²² represents C₁₋₃alkoxyC₂₋₃alkyl);

5) R²⁸ (wherein R²⁸ is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which

5 heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₃alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₃alkyl and C₁₋₄alkylsulphonylC₁₋₄alkyl, and an additional possible substituent is C₁₋₄alkoxycarbonyl);

6) C₁₋₅alkylR²⁸ (wherein R²⁸ is as defined hereinbefore);

7) C₂₋₅alkenylR²⁸ (wherein R²⁸ is as defined hereinbefore);

10 8) C₂₋₅alkynylR²⁸ (wherein R²⁸ is as defined hereinbefore);

9) R²⁹ (wherein R²⁹ represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents on an available carbon atom selected from hydroxy, halogeno, amino, C₁₋₄alkyl,

15 C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, trifluoromethyl, cyano, -CONR³⁰R³¹ and -NR³²COR³³ (wherein R³⁰, R³¹, R³² and R³³, which may be the same or different, each represents hydrogen, C₁₋₄alkyl or C₁₋₃alkoxyC₂₋₃alkyl));

10) C₁₋₅alkylR²⁹ (wherein R²⁹ is as defined hereinbefore);

11) C₂₋₅alkenylR²⁹ (wherein R²⁹ is as defined hereinbefore);

20 12) C₂₋₅alkynylR²⁹ (wherein R²⁹ is as defined hereinbefore);

13) C₁₋₅alkylX⁶R²⁹ (wherein X⁶ represents -O-, -S-, -SO-, -SO₂-, -NR³⁴CO-, -CONR³⁵-, -SO₂NR³⁶-, -NR³⁷SO₂- or -NR³⁸- (wherein R³⁴, R³⁵, R³⁶, R³⁷ and R³⁸ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined hereinbefore);

14) C₂₋₅alkenylX⁷R²⁹ (wherein X⁷ represents -O-, -S-, -SO-, -SO₂-, -NR³⁹CO-, -

25 CONR⁴⁰-, -SO₂NR⁴¹-, -NR⁴²SO₂- or -NR⁴³- (wherein R³⁹, R⁴⁰, R⁴¹, R⁴² and R⁴³ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined hereinbefore);

15) C₂₋₅alkynylX⁸R²⁹ (wherein X⁸ represents -O-, -S-, -SO-, -SO₂-, -NR⁴⁴CO-, -CONR⁴⁵-, -SO₂NR⁴⁶-, -NR⁴⁷SO₂- or -NR⁴⁸- (wherein R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁷ and R⁴⁸ each

30 independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined hereinbefore);

16) $C_{1-3}\text{alkyl}X^9C_{1-3}\text{alkyl}R^{29}$ (wherein X^9 represents -O-, -S-, -SO-, -SO₂-, -NR⁴⁹CO-, -CONR⁵⁰-, -SO₂NR⁵¹-, -NR⁵²SO₂- or -NR⁵³- (wherein R⁴⁹, R⁵⁰, R⁵¹, R⁵² and R⁵³ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined hereinbefore); and

5 17) $C_{1-3}\text{alkyl}X^9C_{1-3}\text{alkyl}R^{28}$ (wherein X⁹ and R²⁸ are as defined hereinbefore); and
additionally R⁵ may be selected from a group:

18) $C_{1-3}\text{alkyl}R^{54}C_{1-3}\text{alkyl}X^9R^{55}$ (wherein X⁹ is as defined hereinbefore and R⁵⁴ and R⁵⁵ are each independently selected from hydrogen, C₁₋₃alkyl, cyclopentyl, cyclohexyl and a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, 10 S and N, which C₁₋₃alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C₁₋₄alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄cyanoalkyl and C₁₋₄alkoxycarbonyl), with the proviso that R⁵⁴ cannot be hydrogen;
and additionally wherein any C₁₋₅alkyl, C₂₋₅alkenyl or C₂₋₅alkynyl group in R⁵X¹- may bear one 15 or more substituents selected from hydroxy, halogeno and amino;
and salts thereof, and prodrugs thereof for example esters, amides and sulphides, preferably esters and amides, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

20 Preferably ring C is a 5-6-membered heteroaromatic moiety which contains 1-3 heteroatoms selected independently from O, N and S.

More preferably ring C is a 5-membered heteroaromatic moiety which contains 1-3 heteroatoms selected independently from O, N and S.

Especially ring C is pyrazolyl.

25 Particularly ring C is pyrazolyl wherein the substituent at the 4-position of the pyrazolyl ring is hydrogen.

Preferably Z is -O- or -S-, especially -O-.

In another preferred embodiment of the invention Z is -O- or -NH-.

30 Preferably R¹ represents a phenyl group, a benzyl group or a 5-6-membered heteroaromatic group with 1-3 heteroatoms, selected independently from O, S and N, (linked via a ring carbon atom), which phenyl, benzyl or heteroaromatic group may be substituted as defined hereinbefore. Preferred 5-6-membered heteroaromatic groups contain one or two N

atoms (for example, pyrrole, pyridine, pyrazole, imidazole, pyrimidine, pyrazine and pyridazine), two N atoms and one S atom (for example 1,2,5- and 1,3,4-thiadiazole), one N and one O atom (for example oxazole, isoxazole and oxazine), one N and one S atom (for example thiazole and isothiazole) and one O or one S atom (furan and thiophene).

5 More preferably R¹ is a phenyl group or a 5-6-membered heteroaromatic group with 1-3 heteroatoms, selected independently from O, S and N, (linked via a ring carbon atom), which phenyl or heteroaromatic group is optionally substituted as hereinbefore defined.

Especially R¹ is phenyl optionally substituted as hereinbefore defined.

10 In another preferred embodiment of the invention R¹ is a phenyl, thienyl or a furyl group which phenyl, thienyl or furyl group is optionally substituted as hereinbefore defined.

In another preferred embodiment of the invention R¹ is a phenyl or a furyl group which phenyl or furyl group is optionally substituted as hereinbefore defined.

15 Preferably the substituents on an available ring carbon atom in R¹ are selected independently from halogeno, C₁₋₂alkyl, C₁₋₂alkoxy, trifluoromethyl, cyano, nitro, C₂₋₃alkanoyl, C₁₋₃alkanoylamino, C₁₋₃alkoxycarbonyl, C₁₋₃alkylsulphonyl, C₁₋₃alkylsulphinyll, C₁₋₃alkylsulphonyl, carbamoyl, N-C₁₋₃alkylcarbamoyl, N,N-di(C₁₋₃alkyl)carbamoyl, aminosulphonyl, N-C₁₋₃alkylaminosulphonyl, N,N-di(C₁₋₃alkyl)aminosulphonyl, C₁₋₃alkylsulphonylamino, and a saturated heterocyclic group selected from morpholino, thiomorpholino, pyrrolidin-1-yl, piperazin-1-yl, piperazin-4-yl, and piperidino which 20 saturated heterocyclic group may be substituted as hereinbefore defined.

More preferably the substituents on an available ring carbon atom in R¹ are selected independently from halogeno, trifluoromethyl, cyano, nitro, C₂₋₃alkanoyl, C₁₋₃alkoxycarbonyl, C₁₋₃alkylsulphinyll, C₁₋₃alkylsulphonyl, carbamoyl, N-C₁₋₃alkylcarbamoyl, N,N-di(C₁₋₃alkyl)carbamoyl, aminosulphonyl, N-C₁₋₃alkylaminosulphonyl, N,N-di(C₁₋₃alkyl)aminosulphonyl, and a saturated heterocyclic group selected from morpholino, thiomorpholino, pyrrolidin-1-yl, piperazin-1-yl, piperazin-4-yl, and piperidino which 25 saturated heterocyclic group is unsubstituted.

In another more preferred embodiment of the invention the substituents on an available ring carbon atom in R¹ are selected independently from C₁₋₂alkyl, C₁₋₂alkoxy, halogeno, trifluoromethyl, cyano, nitro, C₂₋₃alkanoyl, C₁₋₃alkoxycarbonyl, C₁₋₃alkylsulphinyll, C₁₋₃alkylsulphonyl, carbamoyl, N-C₁₋₃alkylcarbamoyl, N,N-di(C₁₋₃alkyl)carbamoyl, aminosulphonyl, N-C₁₋₃alkylaminosulphonyl, N,N-di(C₁₋₃alkyl)aminosulphonyl, and a 30

saturated heterocyclic group selected from morpholino, thiomorpholino, pyrrolidin-1-yl, piperazin-1-yl, piperazin-4-yl, and piperidino which saturated heterocyclic group is unsubstituted.

Preferably n is 1.

5 Preferably m is an integer from 0 to 2, more preferably 1 or 2, most preferably 2.

Advantageously X¹ represents -O-, -S-, -NR⁶CO-, -NR⁹SO₂- or -NR¹⁰- (wherein R⁶, R⁹ and R¹⁰ each independently represents hydrogen, C₁₋₂alkyl or C₁₋₂alkoxyethyl).

Preferably X¹ represents -O-, -S-, -NR⁶CO-, -NR⁹SO₂- (wherein R⁶ and R⁹ each independently represents hydrogen or C₁₋₂alkyl) or NH.

10 More preferably X¹ represents -O-, -S-, -NR⁶CO- (wherein R⁶ represents hydrogen or C₁₋₂alkyl) or NH.

Particularly X¹ represents -O- or -NR⁶CO- (wherein R⁶ represents hydrogen or C₁₋₂alkyl), more particularly -O- or -NHCO-, especially -O-.

15 Advantageously X² represents -O- or NR¹² (wherein R¹² represents hydrogen, C₁₋₃alkyl or C₁₋₂alkoxyethyl).

Advantageously X³ represents -O-, -S-, -SO-, -SO₂-, -NR¹⁷CO-, -NR²⁰SO₂- or -NR²¹- (wherein R¹⁷, R²⁰ and R²¹ each independently represents hydrogen, C₁₋₂alkyl or C₁₋₂alkoxyethyl).

20 Preferably X³ represents -O-, -S-, -SO-, -SO₂- or -NR²¹- (wherein R²¹ represents hydrogen, C₁₋₂alkyl or C₁₋₂alkoxyethyl).

More preferably X³ represents -O- or -NR²¹- (wherein R²¹ represents hydrogen or C₁₋₂alkyl).

Advantageously X⁴ and X⁵ which may be the same or different each represents -O-, -S-, -SO-, -SO₂- or -NR²⁷- (wherein R²⁷ represents hydrogen, C₁₋₃alkyl or C₁₋₂alkoxyethyl).

25 Preferably X⁴ and X⁵ which may be the same or different each represents -O-, -S- or -NR²⁷- (wherein R²⁷ represents hydrogen, C₁₋₂alkyl or C₁₋₂alkoxyethyl).

More preferably X⁴ and X⁵ which may be the same or different each represents -O- or -NH-.

30 Advantageously X⁶ represents -O-, -S- or -NR³⁸- (wherein R³⁸ represents hydrogen, C₁₋₂alkyl or C₁₋₂alkoxyethyl).

Preferably X⁶ represents -O- or -NR³⁸- (wherein R³⁸ represents hydrogen or C₁₋₂alkyl).

Advantageously X⁷ represents -O-, -S- or -NR⁴³- (wherein R⁴³ represents hydrogen, C₁₋₂alkyl or C₁₋₂alkoxyethyl).

Preferably X⁷ represents -O- or -NR⁴³- (wherein R⁴³ represents hydrogen or C₁₋₂alkyl).

Advantageously X⁸ represents -O-, -S- or -NR⁴⁸- (wherein R⁴⁸ represents hydrogen, C₁₋₂alkyl or C₁₋₂alkoxyethyl).

Preferably X⁸ represents -O- or -NR⁴⁸- (wherein R⁴⁸ represents hydrogen or C₁₋₂alkyl).

Advantageously X⁹ represents -O-, -S- or -NR⁵³- (wherein R⁵³ represents hydrogen, C₁₋₂alkyl or C₁₋₂alkoxyethyl).

Preferably X⁹ represents -O- or -NR⁵³- (wherein R⁵³ represents hydrogen or C₁₋₂alkyl).

10 Preferably R²⁸ is pyrrolidinyl, piperazinyl, piperidinyl, morpholino or thiomorpholino (linked preferably via nitrogen) which group may carry 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₃alkyl, C₁₋₃hydroxyalkyl, C₁₋₃alkoxy, C₁₋₂alkoxyC₁₋₃alkyl and C₁₋₂alkylsulphonylC₁₋₃alkyl.

15 Preferably R²⁹ represents a pyridone group or a 5-6-membered aromatic heterocyclic group with 1 to 3 heteroatoms selected from O, N and S, which pyridone group or heterocyclic group may be substituted as hereinbefore defined.

Where R²⁹ is a 5-6-membered aromatic heterocyclic group, it preferably has 1 or 2 heteroatoms, selected from O, N and S, of which more preferably one is N, and may be substituted as hereinbefore defined.

20 R²⁹ is particularly a pyridone, pyridyl, imidazolyl, thiazolyl, thietyl, triazolyl or pyridazinyl group which group may be substituted as hereinbefore defined, more particularly a pyridone, pyridyl, imidazolyl, thiazolyl or triazolyl group, especially a pyridone, pyridyl, imidazolyl or triazolyl group which group may be substituted as hereinbefore defined.

In one embodiment of the invention R²⁹ represents a pyridone, phenyl or 5-6-membered aromatic heterocyclic group with 1 to 3 heteroatoms selected from O, N and S, which group may preferably carry up to 2 substituents, more preferably up to one substituent, selected from the group of substituents as hereinbefore defined.

30 In the definition of R²⁹, conveniently substituents are selected from halogeno, C₁₋₄alkyl, C₁₋₄alkoxy and cyano, more conveniently substituents are selected from chloro, fluoro, methyl and ethyl.

Preferably R⁵⁴ is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group is optionally substituted as hereinbefore defined.

More preferably R⁵⁴ is a 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group is optionally substituted as hereinbefore defined.

In one embodiment of the present invention R⁵⁴ is piperidinyl, pyrrolidinyl or piperazinyl, which group is optionally substituted as hereinbefore defined.

Preferably R⁵⁵ is C₁₋₃alkyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group is optionally substituted as hereinbefore defined.

More preferably R⁵⁵ is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group is optionally substituted as hereinbefore defined.

Especially R⁵⁵ is a group selected from morpholino, pyrrolidin-1-yl, piperidino, piperazin-1-yl and thiomorpholino which group is optionally substituted as hereinbefore defined.

Conveniently R² represents hydroxy, halogeno, nitro, trifluoromethyl, C₁₋₃alkyl, cyano, amino or R⁵X¹- [wherein X¹ is as hereinbefore defined and R⁵ is selected from one of the following seventeen groups:

1) C₁₋₃alkyl which may be unsubstituted or substituted with one or more fluorine atoms, or C₂₋₃alkyl which may be unsubstituted or substituted with one or more groups selected from hydroxy and amino;

2) C₂₋₃alkylX²COR¹¹ (wherein X² is as hereinbefore defined and R¹¹ represents C₁₋₃alkyl, -NR¹³R¹⁴ or -OR¹⁵ (wherein R¹³, R¹⁴ and R¹⁵ which may be the same or different are each C₁₋₂alkyl or C₁₋₂alkoxyethyl));

3) C₂₋₄alkylX³R¹⁶ (wherein X³ is as hereinbefore defined and R¹⁶ represents hydrogen, C₁₋₃alkyl, cyclopentyl, cyclohexyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C₁₋₃alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C₁₋₃alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl and C₁₋₄alkoxy);

4) $C_{2-3}\text{alkyl}X^4C_{2-3}\text{alkyl}X^5R^{22}$ (wherein X^4 and X^5 are as hereinbefore defined and R^{22} represents hydrogen or $C_{1-3}\text{alkyl}$);

5) $C_{1-5}\text{alkyl}R^{56}$ (wherein R^{56} is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group is linked to $C_{1-5}\text{alkyl}$ through a carbon atom and which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, $C_{1-4}\text{alkyl}$, $C_{1-4}\text{hydroxyalkyl}$, $C_{1-4}\text{alkoxy}$, $C_{1-4}\text{alkoxy}C_{1-4}\text{alkyl}$ and $C_{1-4}\text{alkylsulphonyl}C_{1-4}\text{alkyl}$) or $C_{2-5}\text{alkyl}R^{57}$ (wherein R^{57} is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms of which one is N and the other is selected independently from O, S and N, which heterocyclic group is linked to $C_{2-5}\text{alkyl}$ through a nitrogen atom and which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, $C_{1-4}\text{alkyl}$, $C_{1-4}\text{hydroxyalkyl}$, $C_{1-4}\text{alkoxy}$, $C_{1-4}\text{alkoxy}C_{1-4}\text{alkyl}$ and $C_{1-4}\text{alkylsulphonyl}C_{1-4}\text{alkyl}$);

6) $C_{3-4}\text{alkenyl}R^{58}$ (wherein R^{58} represents R^{56} or R^{57} as defined hereinbefore);

7) $C_{3-4}\text{alkynyl}R^{58}$ (wherein R^{58} represents R^{56} or R^{57} as defined hereinbefore);

8) R^{29} (wherein R^{29} is as defined hereinbefore);

9) $C_{1-3}\text{alkyl}R^{29}$ (wherein R^{29} is as defined hereinbefore);

10) $C_{3-5}\text{alkenyl}R^{29}$ (wherein R^{29} is as defined hereinbefore);

11) $C_{3-5}\text{alkynyl}R^{29}$ (wherein R^{29} is as defined hereinbefore);

12) $C_{1-5}\text{alkyl}X^6X^{29}$ (wherein X^6 and R^{29} are as defined hereinbefore);

13) $C_{4-5}\text{alkenyl}X^7R^{29}$ (wherein X^7 and R^{29} are as defined hereinbefore);

14) $C_{4-5}\text{alkynyl}X^8R^{29}$ (wherein X^8 and R^{29} are as defined hereinbefore);

15) $C_{2-5}\text{alkyl}X^9C_{1-2}\text{alkyl}R^{29}$ (wherein X^9 and R^{29} are as defined hereinbefore);

16) R^{28} (wherein R^{28} is as defined hereinbefore); and

17) $C_{2-5}\text{alkyl}X^9C_{1-2}\text{alkyl}R^{28}$ (wherein X^9 and R^{28} are as defined hereinbefore); and

25 additionally R^5 may be selected from a group:

18) $C_{2-3}\text{alkyl}R^{54}C_{1-2}\text{alkyl}IX^9R^{55}$ (wherein X^9 , R^{54} and R^{55} are as defined hereinbefore);

and additionally wherein any $C_{1-5}\text{alkyl}$, $C_{2-5}\text{alkenyl}$ or $C_{2-5}\text{alkynyl}$ group in R^5X^1- may bear one or more substituents selected from hydroxy, halogeno and amino].

Advantageously R^2 represents hydroxy, halogeno, nitro, trifluoromethyl, $C_{1-3}\text{alkyl}$.

30 cyano, amino or R^5X^1- [wherein X^1 is as hereinbefore defined and R^5 is selected from one of the following seventeen groups:

1) C₁₋₄alkyl which may be unsubstituted or substituted with one or more fluorine atoms, or C₂₋₄alkyl which may be unsubstituted or substituted with 1 or 2 groups selected from hydroxy and amino;

2) C₂₋₃alkylX²COR¹¹ (wherein X² is as hereinbefore defined and R¹¹ represents -

5 NR¹³R¹⁴ or

-OR¹⁵ (wherein R¹³, R¹⁴ and R¹⁵ which may be the same or different are each C₁₋₂alkyl or C₁₋₂alkoxyethyl));

10 3) C₂₋₄alkylX³R¹⁶ (wherein X³ is as hereinbefore defined and R¹⁶ is a group selected from C₁₋₃alkyl, cyclopentyl, cyclohexyl, pyrrolidinyl and piperidinyl which group is linked to X³ through a carbon atom and which C₁₋₃alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C₁₋₂alkoxy and which cyclopentyl, cyclohexyl, pyrrolidinyl or piperidinyl group may carry one substituent selected from oxo, hydroxy, halogeno, C₁₋₂alkyl, C₁₋₂hydroxyalkyl and C₁₋₂alkoxy);

15 4) C₂₋₃alkylX⁴C₂₋₃alkylX⁵R²² (wherein X⁴ and X⁵ are as hereinbefore defined and R²² represents hydrogen or C₁₋₃alkyl);

20 5) C₁₋₄alkylR⁵⁹ (wherein R⁵⁹ is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithiolan-2-yl and 1,3-dithian-2-yl, which group is linked to C₁₋₄alkyl through a carbon atom and which group may carry 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₃alkyl, C₁₋₃hydroxyalkyl, C₁₋₃alkoxy, C₁₋₂alkoxyC₁₋₃alkyl and C₁₋₂alkylsulphonylC₁₋₃alkyl) or C₂₋₄alkylR⁶⁰ (wherein R⁶⁰ is a group selected from morpholino, thiomorpholino, pyrrolidin-1-yl, piperazin-1-yl and piperidino which group may carry 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₃alkyl, C₁₋₃hydroxyalkyl, C₁₋₃alkoxy, C₁₋₂alkoxyC₁₋₃alkyl and C₁₋₂alkylsulphonylC₁₋₃alkyl);

25 6) C₃₋₄alkenylR⁶¹ (wherein R⁶¹ represents R⁵⁹ or R⁶⁰ as defined hereinbefore);

7) C₃₋₄alkynylR⁶¹ (wherein R⁶¹ represents R⁵⁹ or R⁶⁰ as defined hereinbefore);

8) R²⁹ (wherein R²⁹ is as defined hereinbefore);

9) C₁₋₄alkylR²⁹ (wherein R²⁹ is as defined hereinbefore);

10) 1-R²⁹prop-1-en-3-yl or 1-R²⁹but-2-en-4-yl (wherein R²⁹ is as defined hereinbefore with the proviso that when R⁵ is 1-R²⁹prop-1-en-3-yl, R²⁹ is linked to the alkenyl group via a carbon atom);

11) 1-R²⁹prop-1-yn-3-yl or 1-R²⁹but-2-yn-4-yl (wherein R²⁹ is as defined hereinbefore with the proviso that when R⁵ is 1-R²⁹prop-1-yn-3-yl, R²⁹ is linked to the alkynyl group via a carbon atom);

12) C_{1,5}alkylX⁶R²⁹ (wherein X⁶ and R²⁹ are as defined hereinbefore);

5 13) 1-(R²⁹X⁷)but-2-en-4-yl (wherein X⁷ and R²⁹ are as defined hereinbefore);

14) 1-(R²⁹X⁸)but-2-yn-4-yl (wherein X⁸ and R²⁹ are as defined hereinbefore);

15) C_{2,3}alkylX⁹C_{1,2}alkylR²⁹ (wherein X⁹ and R²⁹ are as defined hereinbefore);

16) R²⁸ (wherein R²⁸ is as defined hereinbefore); and

17) C_{2,3}alkylX⁹C_{1,2}alkylR²⁸ (wherein X⁹ and R²⁸ are as defined hereinbefore); and

10 additionally R⁵ may be selected from a group:

18) C_{2,3}alkylR⁵⁴C_{1,2}alkylX⁹R⁵⁵ (wherein X⁹, R⁵⁴ and R⁵⁵ are as defined hereinbefore);

and additionally wherein any C_{1,5}alkyl, C_{2,5}alkenyl or C_{2,5}alkynyl group in R⁵X¹- may bear one or more substituents selected from hydroxy, halogeno and amino].

Preferably R² represents hydroxy, halogeno, nitro, trifluoromethyl, C_{1,3}alkyl, cyano,

15 amino or R⁵X¹- [wherein X¹ is as hereinbefore defined and R⁵ is selected from one of the following fifteen groups:

1) C_{1,3}alkyl which may be unsubstituted or substituted with one or more fluorine atoms, or C_{2,3}alkyl which may be unsubstituted or substituted with 1 or 2 groups selected from hydroxy and amino;

20 2) 2-(3,3-dimethylureido)ethyl, 3-(3,3-dimethylureido)propyl, 2-(3-methylureido)ethyl, 3-(3-methylureido)propyl, 2-ureidoethyl, 3-ureidopropyl, 2-(N,N-dimethylcarbamoyloxy)ethyl, 3-(N,N-dimethylcarbamoyloxy)propyl, 2-(N-methylcarbamoyloxy)ethyl, 3-(N-methylcarbamoyloxy)propyl, 2-(carbamoyloxy)ethyl, 3-(carbamoyloxy)propyl;

25 3) C_{2,3}alkylX³R¹⁶ (wherein X³ is as defined hereinbefore and R¹⁶ is a group selected from C_{1,2}alkyl, cyclopentyl, cyclohexyl, pyrrolidinyl and piperidinyl which group is linked to X³ through a carbon atom and which C_{1,2}alkyl group may bear 1 or 2 substituents selected from hydroxy, halogeno and C_{1,2}alkoxy and which cyclopentyl, cyclohexyl, pyrrolidinyl or piperidinyl group may carry one substituent selected from oxo, hydroxy, halogeno, C_{1,2}alkyl, C_{1,2}hydroxyalkyl and C_{1,2}alkoxy);

30 4) C_{2,3}alkylX⁴C_{2,3}alkylX⁵R²² (wherein X⁴ and X⁵ are as hereinbefore defined and R²² represents hydrogen or C_{1,2}alkyl);

5) $C_{1,2}\text{alkyl}R^{59}$ (wherein R^{59} is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithiolan-2-yl and 1,3-dithian-2-yl, which group is linked to $C_{1,2}\text{alkyl}$ through a carbon atom and which group may carry one substituent selected from oxo, hydroxy, halogeno, $C_{1,3}\text{alkyl}$, $C_{1,3}\text{hydroxyalkyl}$, $C_{1,3}\text{alkoxy}$, $C_{1,2}\text{alkoxy}C_{1,3}\text{alkyl}$ and $C_{1,2}\text{alkylsulphonyl}C_{1,3}\text{alkyl}$) or $C_{2,3}\text{alkyl}R^{60}$ (wherein R^{60} is a group selected from morpholino, thiomorpholino, piperidino, piperazin-1-yl and pyrrolidin-1-yl which group may carry one substituent selected from oxo, hydroxy, halogeno, $C_{1,3}\text{alkyl}$, $C_{1,3}\text{hydroxyalkyl}$, $C_{1,3}\text{alkoxy}$, $C_{1,2}\text{alkoxy}C_{1,3}\text{alkyl}$ and $C_{1,2}\text{alkylsulphonyl}C_{1,3}\text{alkyl}$);

6) R^{29} (wherein R^{29} is as defined hereinbefore);

10 7) $C_{1,4}\text{alkyl}R^{29}$ (wherein R^{29} is as defined hereinbefore);

8) 1- R^{29} but-2-en-4-yl (wherein R^{29} is as defined hereinbefore);

9) 1- R^{29} but-2-yn-4-yl (wherein R^{29} is as defined hereinbefore);

10) $C_{1,3}\text{alkyl}X^6R^{29}$ (wherein X^6 and R^{29} are as defined hereinbefore);

11) 1-($R^{29}X^7$)but-2-en-4-yl (wherein X^7 and R^{29} are as defined hereinbefore);

15 12) 1-($R^{29}X^8$)but-2-yn-4-yl (wherein X^8 and R^{29} are as defined hereinbefore);

13) ethyl X^9 methyl R^{29} (wherein X^9 and R^{29} are as defined hereinbefore);

14) R^{28} (wherein R^{28} is as defined hereinbefore); and

15) ethyl X^9 methyl R^{28} (wherein X^9 and R^{28} are as defined hereinbefore); and

additionally R^5 may be selected from a group:

20 16) ethyl R^{54} methyl X^9R^{55} (wherein X^9 , R^{54} and R^{55} are as defined hereinbefore);

and additionally wherein any $C_{1,2}\text{alkyl}$, $C_{2,5}\text{alkenyl}$ or $C_{2,5}\text{alkynyl}$ group in R^5X^1 - may bear one or more substituents selected from hydroxy, halogeno and amino].

More preferably R^2 represents $C_{1,3}\text{alkyl}$, amino or R^5X^1 - [wherein X^1 is as hereinbefore defined and R^5 represents methyl, ethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2-hydroxyethyl,

25 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, 2-(methylsulphonyl)ethyl, 2-

(methylsulphonyl)ethyl, 2-(N,N-dimethylsulphamoyl)ethyl, 2-(N-methylsulphamoyl)ethyl, 2-

sulphamoyleethyl, 2-(N,N-dimethylamino)ethyl, 3-(N,N-dimethylamino)propyl, 2-

morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-

(methylpiperidino)ethyl, 3-(methylpiperidino)propyl, 2-(ethylpiperidino)ethyl, 3-

30 (ethylpiperidino)propyl, 2-((2-methoxyethyl)piperidino)ethyl, 3-((2-

methoxyethyl)piperidino)propyl, 2-((2-methylsulphonyl)ethylpiperidino)ethyl, 3-((2-

methylsulphonyl)ethylpiperidino)propyl, piperidin-3-ylmethyl, piperidin-4-ylmethyl, 2-

(piperidin-3-yl)ethyl, 2-(piperidin-4-yl)ethyl, 3-(piperidin-3-yl)propyl, 3-(piperidin-4-yl)propyl, 2-(methylpiperidin-3-yl)ethyl, 2-(methylpiperidin-4-yl)ethyl, 3-(methylpiperidin-3-yl)propyl, 3-(methylpiperidin-4-yl)propyl, 2-(ethylpiperidin-3-yl)ethyl, 2-(ethylpiperidin-4-yl)ethyl, 3-(ethylpiperidin-3-yl)propyl, 3-(ethylpiperidin-4-yl)propyl, 2-(2-methoxyethyl)piperidin-3-yl)ethyl, 2-((2-methoxyethyl)piperidin-4-yl)ethyl, 3-((2-methoxyethyl)piperidin-3-yl)propyl, 3-((2-methoxyethyl)piperidin-4-yl)propyl, 2-((2-methylsulphonylethyl)piperidin-3-yl)ethyl, 2-((2-methylsulphonylethyl)piperidin-4-yl)ethyl, 3-((2-methylsulphonylethyl)piperidin-3-yl)propyl, 3-((2-methylsulphonylethyl)piperidin-4-yl)propyl, 1-isopropylpiperidin-2-ylmethyl, 1-isopropylpiperidin-3-ylmethyl, 1-isopropylpiperidin-4-ylmethyl, 2-(1-isopropylpiperidin-2-yl)ethyl, 2-(1-isopropylpiperidin-3-yl)ethyl, 2-(1-isopropylpiperidin-4-yl)ethyl, 3-(1-isopropylpiperidin-2-yl)propyl, 3-(1-isopropylpiperidin-3-yl)propyl, 3-(1-isopropylpiperidin-4-yl)propyl, 2-(piperazin-1-yl)ethyl, 3-(piperazin-1-yl)propyl, 2-(pyrrolidin-1-yl)ethyl, 3-(pyrrolidin-1-yl)propyl, (1,3-dioxolan-2-yl)methyl, 2-(1,3-dioxolan-2-yl)ethyl, 2-(2-methoxyethylamino)ethyl, 2-(2-hydroxyethylamino)ethyl, 3-(2-methoxyethylamino)propyl, 2-methylthiazol-4-ylmethyl, 2-acetamidothiazol-4-ylmethyl, 1-methylimidazol-2-ylmethyl, 2-(imidazol-1-yl)ethyl, 2-(2-methylimidazol-1-yl)ethyl, 2-(2-ethylimidazol-1-yl)ethyl, 3-(2-methylimidazol-1-yl)propyl, 3-(2-ethylimidazol-1-yl)propyl, 2-(1,2,3-triazol-1-yl)ethyl, 2-(1,2,3-triazol-2-yl)ethyl, 2-(1,2,4-triazol-1-yl)ethyl, 2-(1,2,4-triazol-4-yl)ethyl, 4-pyridylmethyl, 2-(4-pyridyl)ethyl, 3-(4-pyridyl)propyl, 2-(4-pyridyloxy)ethyl, 2-(4-pyridylamino)ethyl, 2-(4-oxo-1,4-dihydro-1-pyridyl)ethyl, 2-thiomorpholinoethyl, 3-thiomorpholinopropyl, 2-(2-methoxyethoxy)ethyl, 2-(4-methylpiperazin-1-yl)ethyl, 3-(4-methylpiperazin-1-yl)propyl, 3-(methylsulphanyl)propyl, 3-(methylsulphonyl)propyl, 2-(5-methyl-1,2,4-triazol-1-yl)ethyl, morpholino, 2-((N-(1-methylimidazol-4-ylsulphonyl)-N-methyl)amino)ethyl, 2-((N-methyl-N-4-pyridyl)amino)ethyl or 3-(4-oxidomorpholino)propyl, and additionally R⁵ may represent 2-(2-methoxyethoxy)ethyl, 1-methylpiperidin-4-ylmethyl, 1-(2-methylsulphonylethyl)piperidin-4-ylmethyl, 1-(2-pyrrolidinylethyl)piperidin-4-ylmethyl, 1-(3-pyrrolidinylpropyl)piperidin-4-ylmethyl, 1-(2-piperidinylethyl)piperidin-4-ylmethyl, 1-(3-piperidinylpropyl)piperidin-4-ylmethyl, 1-(2-morpholinoethyl)piperidin-4-ylmethyl, 1-(3-morpholinopropyl)piperidin-4-ylmethyl, 1-(2-thiomorpholinoethyl)piperidin-4-ylmethyl, 1-

(3-thiomorpholinopropyl)piperidin-4-ylmethyl, 1-(2-azetidinylethyl)piperidin-4-ylmethyl or 1-(3-azetidinylpropyl)piperidin-4-ylmethyl].

In another aspect R² represents methoxy, 2-methoxyethoxy, 2-(2-methoxyethoxy)ethoxy, 3-methoxypropoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, 2-(tetrahydropyran-4-yloxy)ethoxy, 3-(tetrahydropyran-4-yloxy)propoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy 2-(1,1-dioxothiomorpholino)ethoxy, 3-(1,1-dioxothiomorpholino)propoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, 2-(N-methoxyacetyl-N-methylamino)ethoxy, 3-(N-methoxyacetyl-N-methylamino)propoxy, N-methylpiperidin-3-ylmethoxy, 4-(pyrrolidin-1-yl)but-2-en-yloxy, 2-(2-oxopyrrolidin-1-yl)ethoxy, 3-(2-oxopyrrolidin-1-yl)propoxy, 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propoxy, 2-(2-(pyrrolidin-1-yl)ethoxy)ethoxy, 2-(2-(4-methylpiperazin-1-yl)ethoxy)ethoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-(methylpiperidino)ethoxy, 3-(methylpiperidino)propoxy, 2-(ethylpiperidino)ethoxy, 3-(ethylpiperidino)propoxy, 2-((2-methoxyethyl)piperidino)ethoxy, 3-((2-methoxyethyl)piperidino)propoxy, 2-((2-methylsulphonyl)ethylpiperidino)ethoxy, 3-((2-methylsulphonyl)ethylpiperidino)propoxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-(piperidin-3-yl)ethoxy, 2-(piperidin-4-yl)ethoxy, 3-(piperidin-3-yl)propoxy, 3-(piperidin-4-yl)propoxy, 2-(methylpiperidin-3-yl)ethoxy, 2-(methylpiperidin-4-yl)ethoxy, 3-(methylpiperidin-3-yl)propoxy, 3-(methylpiperidin-4-yl)propoxy, 2-(ethylpiperidin-3-yl)ethoxy, 2-(ethylpiperidin-4-yl)ethoxy, 3-(ethylpiperidin-3-yl)propoxy, 3-(ethylpiperidin-4-yl)propoxy, 2-((2-methoxyethyl)piperidin-3-yl)ethoxy, 2-((2-methoxyethyl)piperidin-4-yl)ethoxy, 3-((2-methoxyethyl)piperidin-3-yl)propoxy, 3-((2-methoxyethyl)piperidin-4-yl)propoxy, 2-((2-methylsulphonylethyl)piperidin-3-yl)ethoxy, 2-((2-methylsulphonylethyl)piperidin-4-yl)ethoxy, 3-((2-methylsulphonylethyl)piperidin-4-yl)propoxy, 1-isopropylpiperidin-2-ylmethoxy, 1-isopropylpiperidin-3-ylmethoxy, 1-isopropylpiperidin-4-ylmethoxy, 2-(1-isopropylpiperidin-2-yl)ethoxy, 2-(1-isopropylpiperidin-3-yl)ethoxy, 2-(1-isopropylpiperidin-4-yl)ethoxy, 3-(1-isopropylpiperidin-2-yl)propoxy, 3-(1-isopropylpiperidin-3-yl)propoxy or 3-(1-isopropylpiperidin-4-yl)propoxy, and additionally R² may represent 3-(4-methylpiperazin-1-yl)propoxy, 1-methylpiperidin-4-ylmethoxy, 1-(2-methylsulphonylethyl)piperidin-4-ylmethoxy, 1-(2-pyrrolidinylethyl)piperidin-4-ylmethoxy, 1-(3-pyrrolidinylpropyl)piperidin-

4-ylmethoxy, 1-(2-piperidinylethyl)piperidin-4-ylmethoxy, 1-(3-piperidinylpropyl)piperidin-4-ylmethoxy, 1-(2-morpholinoethyl)piperidin-4-ylmethoxy, 1-(3-morpholinopropyl)piperidin-4-ylmethoxy, 1-(2-thiomorpholinoethyl)piperidin-4-ylmethoxy, 1-(3-thiomorpholinopropyl)piperidin-4-ylmethoxy, 1-(2-azetidinylethyl)piperidin-4-ylmethoxy or 5 1-(3-azetidinylpropyl)piperidin-4-ylmethoxy.

In another aspect R² represents 2-methoxyethoxy, 2-(2-methoxyethoxy)ethoxy, 3-methoxypropoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, 2-(tetrahydropyran-4-yloxy)ethoxy, 3-(tetrahydropyran-4-yloxy)propoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy 2-(1,1-dioxothiomorpholino)ethoxy, 3-(1,1-dioxothiomorpholino)propoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, 2-(N-methoxyacetyl-N-methylamino)ethoxy, 3-(N-methoxyacetyl-N-methylamino)propoxy, N-methylpiperidin-3-ylmethoxy, 4-(pyrrolidin-1-yl)but-2-en-yloxy, 2-(2-oxopyrrolidin-1-yl)ethoxy, 3-(2-oxopyrrolidin-1-yl)propoxy, 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propoxy, 2-(2-(pyrrolidin-1-yl)ethoxy)ethoxy, 2-(2-(4-methylpiperazin-1-yl)ethoxy)ethoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-(methylpiperidino)ethoxy, 3-(methylpiperidino)propoxy, 2-(ethylpiperidino)ethoxy, 3-(ethylpiperidino)propoxy, 2-((2-methoxyethyl)piperidino)ethoxy, 3-((2-methoxyethyl)piperidino)propoxy, 2-((2-methylsulphonyl)ethylpiperidino)ethoxy, 3-((2-methylsulphonyl)ethylpiperidino)propoxy, 20 piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-(piperidin-3-yl)ethoxy, 2-(piperidin-4-yl)ethoxy, 3-(piperidin-3-yl)propoxy, 3-(piperidin-4-yl)propoxy, 2-(methylpiperidin-3-yl)ethoxy, 2-(methylpiperidin-4-yl)ethoxy, 3-(methylpiperidin-3-yl)propoxy, 3-(methylpiperidin-4-yl)propoxy, 2-(ethylpiperidin-3-yl)ethoxy, 2-(ethylpiperidin-4-yl)ethoxy, 3-(ethylpiperidin-3-yl)propoxy, 3-(ethylpiperidin-4-yl)propoxy, 2-((2-methoxyethyl)piperidin-3-yl)ethoxy, 2-((2-methoxyethyl)piperidin-3-yl)propoxy, 3-((2-methoxyethyl)piperidin-4-yl)propoxy, 2-((2-methylsulphonylethyl)piperidin-3-yl)ethoxy, 2-((2-methylsulphonylethyl)piperidin-4-yl)ethoxy, 3-((2-methylsulphonylethyl)piperidin-3-yl)propoxy, 3-((2-methylsulphonylethyl)piperidin-4-yl)propoxy, 1-isopropylpiperidin-2-ylmethoxy, 1-25 isopropylpiperidin-3-ylmethoxy, 1-isopropylpiperidin-4-ylmethoxy, 2-(1-isopropylpiperidin-2-yl)ethoxy, 2-(1-isopropylpiperidin-3-yl)ethoxy, 2-(1-isopropylpiperidin-4-yl)ethoxy, 3-(1-isopropylpiperidin-2-yl)propoxy, 3-(1-isopropylpiperidin-3-yl)propoxy or 3-(1-

isopropylpiperidin-4-yl)propoxy, and additionally R² may represent 3-(4-methylpiperazin-1-yl)propoxy, 1-methylpiperidin-4-ylmethoxy, 1-(2-methylsulphonylethyl)piperidin-4-ylmethoxy, 1-(2-pyrrolidinylethyl)piperidin-4-ylmethoxy, 1-(3-pyrrolidinylpropyl)piperidin-4-ylmethoxy, 1-(2-piperidinylethyl)piperidin-4-ylmethoxy, 1-(3-piperidinylpropyl)piperidin-4-ylmethoxy, 1-(2-morpholinoethyl)piperidin-4-ylmethoxy, 1-(3-morpholinopropyl)piperidin-4-ylmethoxy, 1-(2-thiomorpholinoethyl)piperidin-4-ylmethoxy, 1-(3-thiomorpholinopropyl)piperidin-4-ylmethoxy, 1-(2-azetidinylethyl)piperidin-4-ylmethoxy or 1-(3-azetidinylpropyl)piperidin-4-ylmethoxy.

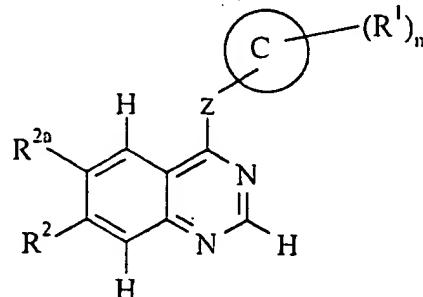
Where one of the R² substituents is R⁵X¹- the substituent R⁵X¹- is preferably at the 6-10 or 7-position of the quinazoline ring, more preferably at the 7-position of the quinazoline ring.

When one of the R² substituents is at the 6-position of the quinazoline ring it is preferably halogeno, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkylsulphanyl or -NR³R⁴ (wherein R³ and R⁴ are as defined hereinbefore). Another preferred value for R² at the 6-position of the quinazoline ring is hydrogen.

15 When one of the R² substituents is at the 6-position of the quinazoline ring it is more preferably C₁₋₃alkoxy, especially methoxy.

In another aspect of the present invention there is provided the use of compounds of the formula Ia:

20



25

(Ia)

wherein:

ring C, R¹, R², n and Z are as defined hereinbefore with the proviso that R² is not hydrogen; and

30 R^{2a} represents halogeno, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkylthio, -NR^{3a}R^{4a} (wherein R^{3a} and R^{4a}, which may be the same or different, each represents hydrogen or C₁₋₃alkyl), or R^{5a}(CH₂)_{za}X^{1a} (wherein R^{5a} is a 5- or 6-membered saturated heterocyclic group with 1-2

heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl and C₁₋₄alkoxy. za is an integer from 0 to 4 and X^{1a} represents a direct bond, -O-, -CH₂-, -S-, -SO-, -SO₂-, -NR^{6a}CO-, -CONR^{7a}-, -SO₂NR^{8a}-, -NR^{9a}SO₂- or -NR^{10a}- (wherein R^{6a}, R^{7a}, R^{8a}, R^{9a} and 5 R^{10a} each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl); or R^{2a} represents hydrogen);

and salts thereof, and prodrugs thereof for example esters, amides and sulphides, preferably esters and amides, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such 10 as humans.

Advantageously X^{1a} represents -O-, -S-, -NR^{6a}CO-, -NR^{9a}SO₂- or -NR^{10a}- (wherein R^{6a}, R^{9a} and R^{10a} each independently represents hydrogen, C₁₋₂alkyl or C₁₋₂alkoxyethyl).

Preferably X^{1a} represents -O-, -S-, -NR^{6a}CO-, -NR^{9a}SO₂- (wherein R^{6a} and R^{9a} each independently represents hydrogen or C₁₋₂alkyl) or NH.

15 More preferably X^{1a} represents -O-, -S-, -NR^{6a}CO- (wherein R^{6a} represents hydrogen or C₁₋₂alkyl) or NH.

Particularly X^{1a} represents -O- or -NR^{6a}CO- (wherein R^{6a} represents hydrogen or C₁₋₂alkyl), more particularly -O- or -NHCO-, especially -O-.

Preferably za is an integer from 1 to 3.

20 Preferably R^{5a} is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, morpholino and thiomorpholino which group may carry 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₂alkyl, C₁₋₂hydroxyalkyl and C₁₋₂alkoxy.

Advantageously R^{2a} represents C₁₋₃alkyl, C₁₋₃alkoxy, amino or R^{5a}(CH₂)_{za}X^{1a} (wherein R^{5a}, X^{1a} and za are as defined hereinbefore). Another advantageous value of R^{2a} is hydrogen.

25 Preferably R^{2a} is methyl, ethyl, methoxy, ethoxy or R^{5a}(CH₂)_{za}X^{1a} (wherein R^{5a}, X^{1a} and za are as defined hereinbefore). Another preferred value of R^{2a} is hydrogen.

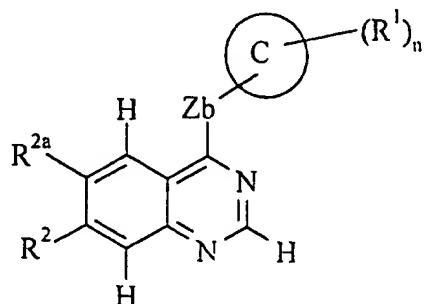
More preferably R^{2a} is methyl, ethyl, methoxy, ethoxy or R^{5a}(CH₂)_{za}X^{1a} (wherein R^{5a} is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, morpholino and thiomorpholino which group may carry 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₂alkyl, C₁₋₂hydroxyalkyl and C₁₋₂alkoxy, X^{1a} is -O-, -S-, -NR^{6a}CO-, -NR^{9a}SO₂- (wherein R^{6a} and R^{9a} each independently represents hydrogen or C₁₋₂alkyl) or NH, and za is an integer from 1 to 3). Another more preferred value of R^{2a} is hydrogen.

- 20 -

Particularly R^{2a} represents methyl, methoxy or R^{5a}(CH₂)_{za}X^{1a} (wherein R^{5a}, X^{1a} and za are as defined hereinbefore).

More particularly R^{2a} represents methoxy.

In a further aspect of the present invention there is provided the use of compounds of
5 the formula Ib:



10

15 wherein:

ring C, R¹, R², R^{2a} and n are as defined hereinbefore with the proviso that R² is not hydrogen; and

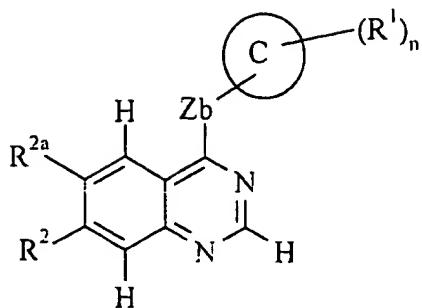
Zb is -O- or -S-;

and salts thereof, and prodrugs thereof for example esters, amides and sulphides,
20 preferably esters and amides, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

Preferably Zb is -O-.

According to another aspect of the present invention there are provided compounds of
25 the formula II:

30



(II)

wherein:

ring C, R¹, R², R^{2a}, Zb and n are as defined hereinbefore with the proviso that R² does

10 not have any of the following values:

hydrogen, substituted or unsubstituted C₁₋₅alkyl, halogeno, C₁₋₅alkoxy, phenoxy or phenylC₁₋₅alkoxy;

and salts thereof, and prodrugs thereof for example esters, amides and sulphides, preferably esters and amides.

15 Preferred compounds of the present invention include

4-(5-benzylpyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

7-(2-methoxyethoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline,

4-(5-butylpyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

6-methoxy-7-(3-morpholinopropoxy)-4-(5-propylpyrazol-3-yloxy)quinazoline,

20 4-(5-methoxymethylpyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

6-methoxy-7-(3-morpholinopropoxy)-4-(5-(pent-3-en-1-yl)pyrazol-3-yloxy)quinazoline,

6-methoxy-7-(3-morpholinopropoxy)-4-(5-(3-pyridyl)pyrazol-3-yloxy)quinazoline,

4-(5-isobutylpyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline and

4-(5-(2-cyclopentylethyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline

25 and salts thereof especially hydrochloride salts thereof and prodrugs thereof for example

esters, amides and sulphides.

More preferred compounds of the present invention include

4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline,

30 4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline,

- 6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline,
4-(5-(3-furyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
6,7-dimethoxy-4-(5-phenylpyrazol-3-yloxy)quinazoline,
6-methoxy-7-(3-morpholinopropoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline,
5 4-(5-(2-fluorophenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
6-methoxy-7-(3-morpholinopropoxy)-4-(5-(3-nitrophenyl)pyrazol-3-yloxy)quinazoline,
6-methoxy-7-(3-morpholinopropoxy)-4-(5-(4-nitrophenyl)pyrazol-3-yloxy)quinazoline,
6-methoxy-7-(3-morpholinopropoxy)-4-(5-(4-pyridyl)pyrazol-3-yloxy)quinazoline,
7-(2-(imidazol-1-yl)ethoxy)-6-methoxy-4-(5-phenylpyrazol-3-yloxy)quinazoline and
10 4-(5-(4-fluorophenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline
and salts thereof especially hydrochloride salts thereof and prodrugs thereof for example
esters, amides and sulphides.

Especially preferred compounds of the present invention include

- 4-(5-(4-chlorophenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
15 6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline,
6-methoxy-7-(2-methoxyethoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline and
6-methoxy-7-(2-methoxyethoxy)-4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)quinazoline
and salts thereof especially hydrochloride salts thereof and prodrugs thereof for example
esters, amides and sulphides.

- 20 According to another especially preferred aspect of the present invention there is provided the use of a compound selected from:

- 6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)-4-(5-phenylpyrazol-3-ylamino)quinazoline
and
6,7-dimethoxy-4-(5-phenylpyrazol-3-yloxy)quinazoline
25 or a salt thereof, or a prodrug thereof for example an ester or amide, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

- According to another more preferred aspect of the present invention there is provided the use of a compound selected from:
30 6-methoxy-4-(5-(4-methoxyphenyl)pyrazol-3-ylamino)-7-(1-methylpiperidin-4-ylmethoxy)quinazoline,

4-(5-(4-chlorophenyl)pyrazol-3-ylamino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline and

6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)-4-(5-(4-methylphenyl)pyrazol-3-ylamino)quinazoline,

- 5 or a salt thereof, or a prodrug thereof for example an ester or amide, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

According to another preferred aspect of the present invention there is provided the use of a compound selected from:

- 10 6,7-dimethoxy-4-(5-phenylpyrazol-3-ylamino)quinazoline,
4-(5-(3,4-dichlorophenyl)pyrazol-3-ylamino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline,
6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)-4-(5-(3-trifluoromethylphenyl)pyrazol-3-ylamino)quinazoline and
- 15 4-(5-cyclopropyl)pyrazol-3-ylamino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline
or a salt thereof, or a prodrug thereof for example an ester or amide, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

- 20 Another especially preferred group of compounds of the present invention includes
4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline.

- 25 4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline,
6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline,
4-(5-(3-furyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
6-methoxy-7-(3-morpholinopropoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline,
7-(2-(imidazol-1-yl)ethoxy)-6-methoxy-4-(5-phenylpyrazol-3-yloxy)quinazoline,
4-(5-(4-chlorophenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
30 6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline,
6-methoxy-7-(2-methoxyethoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline,

4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)-6-methoxy-7-(2-(1,2,3-triazol-1-yl)ethoxy)quinazoline and
4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)-6-methoxy-7-(1-(2-methylsulphonylethyl)piperidin-4-yloxy)quinazoline,

- 5 and salts thereof especially hydrochloride salts thereof and prodrugs thereof for example esters and amides.

Another more preferred group of compounds of the present invention includes
7-(2-methoxyethoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline,
4-(5-(2-fluorophenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
10 6-methoxy-7-(3-morpholinopropoxy)-4-(5-(3-nitrophenyl)pyrazol-3-yloxy)quinazoline,
6-methoxy-7-(3-morpholinopropoxy)-4-(5-(4-nitrophenyl)pyrazol-3-yloxy)quinazoline,
6-methoxy-7-(3-morpholinopropoxy)-4-(5-(4-pyridyl)pyrazol-3-yloxy)quinazoline,
4-(5-(4-fluorophenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline, and
6-methoxy-7-(2-methoxyethoxy)-4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)quinazoline,

- 15 and salts thereof especially hydrochloride salts thereof and prodrugs thereof for example esters and amides.

Another preferred group of compounds of the present invention includes
4-(5-benzylpyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
4-(5-butylpyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
20 6-methoxy-7-(3-morpholinopropoxy)-4-(5-propylpyrazol-3-yloxy)quinazoline,
4-(5-methoxymethylpyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
6-methoxy-7-(3-morpholinopropoxy)-4-(5-(pent-3-en-1-yl)pyrazol-3-yloxy)quinazoline,
6-methoxy-7-(3-morpholinopropoxy)-4-(5-(3-pyridyl)pyrazol-3-yloxy)quinazoline,
4-(5-isobutylpyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
25 4-(5-(2-cyclopentylethyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
4-(5-(3,4-dimethoxyphenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
6-methoxy-7-(3-morpholinopropoxy)-4-(5-(pent-3-en-1-yl)pyrazol-3-yloxy)quinazoline,
6-methoxy-7-(3-morpholinopropoxy)-4-(5-(2-phenylethyl)pyrazol-3-yloxy)quinazoline,
30 4-(5-ethylpyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline and
4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline,

and salts thereof especially hydrochloride salts thereof and prodrugs thereof for example esters and amides.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined' or 'defined hereinbefore' the said group encompasses the first occurring and broadest definition as well as each and all of the preferred definitions for that group.

In this specification unless stated otherwise the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. An analogous convention applies to other generic

10 terms. Unless otherwise stated the term "alkyl" advantageously refers to chains with 1-6 carbon atoms, preferably 1-4 carbon atoms. The term "alkoxy" as used herein, unless stated otherwise includes "alkyl"-O- groups in which "alkyl" is as hereinbefore defined. The term "aryl" as used herein unless stated otherwise includes reference to a C₆₋₁₀ aryl group which may, if desired, carry one or more substituents selected from halogeno, alkyl, alkoxy, nitro,

15 trifluoromethyl and cyano, (wherein alkyl and alkoxy are as hereinbefore defined). The term "aryloxy" as used herein unless otherwise stated includes "aryl"-O-groups in which "aryl" is as hereinbefore defined. The term "sulphonyloxy" as used herein refers to alkylsulphonyloxy and arylsulphonyloxy groups in which "alkyl" and "aryl" are as hereinbefore defined. The term "alkanoyl" as used herein unless otherwise stated includes formyl and alkylC=O groups

20 in which "alkyl" is as defined hereinbefore, for example C₂alkanoyl is ethanoyl and refers to CH₃C=O, C₃alkanoyl is formyl and refers to CHO. In this specification unless stated otherwise the term "alkenyl" includes both straight and branched chain alkenyl groups but references to individual alkenyl groups such as 2-but enyl are specific for the straight chain version only. Unless otherwise stated the term "alkenyl" advantageously refers to chains with

25 2-5 carbon atoms, preferably 3-4 carbon atoms. In this specification unless stated otherwise the term "alkynyl" includes both straight and branched chain alkynyl groups but references to individual alkynyl groups such as 2-butynyl are specific for the straight chain version only.

Unless otherwise stated the term "alkynyl" advantageously refers to chains with 2-5 carbon atoms, preferably 3-4 carbon atoms.

30 For the avoidance of doubt it is to be understood that where R² has a value of substituted or unsubstituted C₁₋₅alkyl, it has been selected from C₁₋₅alkyl or from R⁵X¹.

wherein R⁵ has been selected from group 1) as defined hereinbefore and wherein X¹ has the value -CH₂- or is a direct bond.

Within the present invention it is to be understood that a compound of the formula I or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which inhibits VEGF receptor tyrosine kinase activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been possible to show graphically herein.

It will be appreciated that compounds of the formula I or a salt thereof may possess an asymmetric carbon atom. Such an asymmetric carbon atom is also involved in the tautomerism described above, and it is to be understood that the present invention encompasses any chiral form (including both pure enantiomers and racemic mixtures) as well as any tautomeric form which inhibits VEGF receptor tyrosine kinase activity, and is not to be limited merely to any one tautomeric form or chiral form utilised within the formulae drawings. It is to be understood that the invention encompasses all optical and diastereomers which inhibit VEGF receptor tyrosine kinase activity.

It is also to be understood that certain compounds of the formula I and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which inhibit VEGF receptor tyrosine kinase activity.

For the avoidance of any doubt, it is to be understood that when X¹ is, for example, a group of formula -NR⁶CO-, it is the nitrogen atom bearing the R⁶ group which is attached to the quinazoline ring and the carbonyl (CO) group is attached to R⁵, whereas when X¹ is, for example, a group of formula -CONR⁷-, it is the carbonyl group which is attached to the quinazoline ring and the nitrogen atom bearing the R⁷ group is attached to R⁵. A similar convention applies to the other two atom X¹ linking groups such as -NR⁹SO₂- and -SO₂NR⁸. When X¹ is -NR¹⁰- it is the nitrogen atom bearing the R¹⁰ group which is linked to the quinazoline ring and to R⁵. An analogous convention applies to other groups. It is further to be understood that when X¹ represents -NR¹⁰- and R¹⁰ is C_{1,3}alkoxyC_{2,3}alkyl it is the C_{2,3}alkyl

moiety which is linked to the nitrogen atom of X¹ and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that in a compound of the formula I when R⁵ is, for example, a group of formula C₁₋₅alkylX⁹C₁₋₅alkylR²⁹, it is the terminal C₁₋₅alkyl moiety which is linked to X¹, similarly when R⁵ is, for example, a group of formula C₂₋₅alkenylR²⁸ it is the C₂₋₅alkenyl moiety which is linked to X¹ and an analogous convention applies to other groups. When R⁵ is a group 1-R²⁹prop-1-en-3-yl it is the first carbon to which the group R²⁹ is attached and it is the third carbon which is linked to X¹ and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that when R²⁹ carries a C₁₋₄aminoalkyl substituent it is the C₁₋₄alkyl moiety which is attached to R²⁹ whereas when R²⁹ carries a C₁₋₄alkylamino substituent it is the amino moiety which is attached to R²⁹ and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that when R²⁸ carries a C₁₋₄alkoxyC₁₋₄alkyl substituent it is the C₁₋₄alkyl moiety which is attached to R²⁸ and an analogous convention applies to other groups.

The present invention relates to the compounds of formula I as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula I and their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the invention may, for example, include acid addition salts of the compounds of formula I as hereinbefore defined which are sufficiently basic to form such salts. Such acid addition salts include for example salts with inorganic or organic acids affording pharmaceutically acceptable anions such as with hydrogen halides (especially hydrochloric or hydrobromic acid of which hydrochloric acid is particularly preferred) or with sulphuric or phosphoric acid, or with trifluoroacetic, citric or maleic acid. In addition where the compounds of formula I are sufficiently acidic, pharmaceutically acceptable salts may be formed with an inorganic or organic base which affords a pharmaceutically acceptable cation. Such salts with inorganic or organic bases include for example an alkali metal salt, such as a sodium or potassium salt, an alkaline earth metal salt such as a calcium or magnesium salt, an ammonium salt or for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

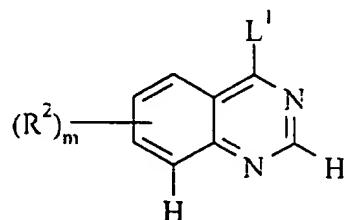
A compound of the formula I, or salt thereof, and other compounds of the invention (as hereinafter defined) may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes include, for example, those illustrated in European Patent Applications Publication Nos. 0520722, 0566226, 0602851 and 5 0635498 and in International Patent Applications Publication Nos. WO 97/22596, WO 97/30035, WO 97/32856, WO 97/42187 and WO 98/13354. Such processes also include, for example, solid phase synthesis. Such processes, are provided as a further feature of the invention and are as described hereinafter. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is 10 described within the accompanying non-limiting Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

Thus, the following processes (a) to (f) and (i) to (vi) constitute further features of the present invention.

15 Synthesis of Compounds of Formula I

(a) Compounds of the formula I and salts thereof may be prepared by the reaction of a compound of the formula III:

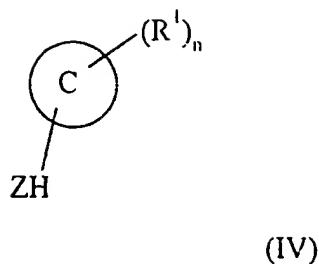
20



(III)

25

(wherein R² and m are as defined hereinbefore and L¹ is a displaceable moiety), with a compound of the formula IV:



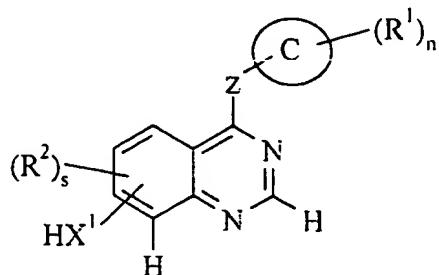
5 (wherein ring C, R¹, Z and n are as defined hereinbefore) to obtain compounds of the formula I and salts thereof. A convenient displaceable moiety L¹ is, for example, a halogeno, alkoxy (preferably C₁₋₄ alkoxy), aryloxy, alkylsulphonyl, arylsulphonyl, alkoxyalkylsulphonyl or sulphonyloxy group, for example a chloro, bromo, methoxy, phenoxy, methylsulphonyl, 2-methoxyethylsulphonyl, methanesulphonyloxy or toluene-4-sulphonyloxy group.

10 The reaction is advantageously effected in the presence of a base. Such a base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, tetramethylguanidine or for example, an alkali metal or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide. Alternatively such a base is, for example, an alkali metal hydride, for example sodium hydride, or an alkali metal or alkaline earth metal amide, for example sodium amide, sodium bis(trimethylsilyl)amide, potassium amide or potassium bis(trimethylsilyl)amide. The reaction is preferably effected in the presence of an inert solvent or diluent, for example an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic hydrocarbon solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethyl sulphoxide. The reaction is conveniently effected at a temperature in the range, for example, 10 to 150°C, preferably in the range 20 to 90°C.

When it is desired to obtain the acid salt, the free base may be treated with an acid 25 such as a hydrogen halide, for example hydrogen chloride, sulphuric acid, a sulphonic acid, for example methane sulphonic acid, or a carboxylic acid, for example acetic or citric acid, using a conventional procedure.

(b) Production of those compounds of formula I and salts thereof wherein at least one R² is R⁵X¹ wherein R⁵ is as defined hereinbefore and X¹ is -O-, -S-, -OCO- or -NR¹⁰- (wherein

R^{10} independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) can be achieved by the reaction, conveniently in the presence of a base (as defined hereinbefore in process (a)) of a compound of the formula V:



10

(V)

(wherein ring C, Z, R^1 , R^2 and n are as hereinbefore defined and X^1 is as hereinbefore defined in this section and s is an integer from 0 to 2) with a compound of formula VI:

15

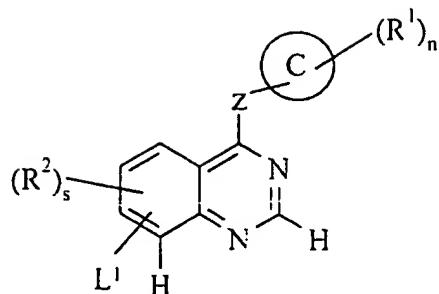
 R^5-L^1 (VI)

(wherein R^5 and L^1 are as hereinbefore defined), L^1 is a displaceable moiety for example a halogeno or sulphonyloxy group such as a bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group, or L^1 may be generated in situ from an alcohol under standard

20 Mitsunobu conditions ("Organic Reactions", John Wiley & Sons Inc, 1992, vol 42, chapter 2, David L Hughes). The reaction is preferably effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)), advantageously at a temperature in the range, for example 10 to 150°C, conveniently at about 50°C.

25 (c) Compounds of the formula I and salts thereof wherein at least one R^2 is R^5X^1 wherein R^5 is as defined hereinbefore and X^1 is -O-, -S-, -OCO- or -NR¹⁰- (wherein R^{10} represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) may be prepared by the reaction of a compound of the formula VII:

5



10



- (wherein L¹, R¹, R², R⁵, ring C, Z, n and s are all as hereinbefore defined and X¹ is as hereinbefore defined in this section). The reaction may conveniently be effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)), advantageously at a temperature in the range, for example 10 to 150°C, conveniently at about 100°C.
- (d) Compounds of the formula I and salts thereof wherein at least one R² is R⁵X¹ wherein X¹ is as defined hereinbefore and R⁵ is C₁₋₃alkylR⁶², wherein R⁶² is selected from one of the following nine groups:

- 1) X¹⁰C₁₋₃alkyl (wherein X¹⁰ represents -O-, -S-, -SO₂-, -NR⁶³CO- or -NR⁶⁴SO₂- (wherein R⁶³ and R⁶⁴ which may be the same or different are each hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl);
- 2) NR⁶⁵R⁶⁶ (wherein R⁶⁵ and R⁶⁶ which may be the same or different are each hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl);
- 3) X¹¹C₁₋₃alkylX⁵R²² (wherein X¹¹ represents -O-, -S-, -SO₂-, -NR⁶⁷CO-, -NR⁶⁸SO₂- or -NR⁶⁹- (wherein R⁶⁷, R⁶⁸, and R⁶⁹ which may be the same or different are each hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and X⁵ and R²² are as defined hereinbefore);
- 4) R²⁸ (wherein R²⁸ is as defined hereinbefore);
- 5) X¹²R²⁹ (wherein X¹² represents -O-, -S-, -SO₂-, -NR⁷⁰CO-, -NR⁷¹SO₂-, or -NR⁷²- (wherein R⁷⁰, R⁷¹, and R⁷² which may be the same or different are each hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined hereinbefore);

6) $X^{13}C_{1-5}$ alkylR²⁹, preferably $X^{13}C_{1-3}$ alkylR²⁹, (wherein X¹³ represents -O-, -S-, -SO₂-, -NR⁷³CO-, -NR⁷⁴SO₂- or -NR⁷⁵- (wherein R⁷³, R⁷⁴ and R⁷⁵ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined hereinbefore);

7) R²⁹ (wherein R²⁹ is as defined hereinbefore);

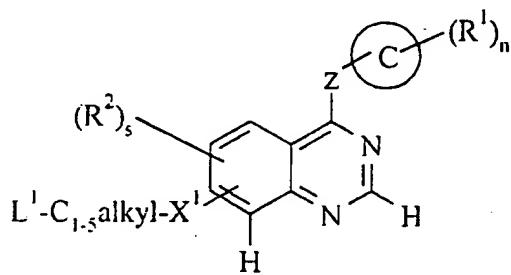
5 8) $X^{14}C_{1-3}$ alkylR²⁸ (wherein X¹⁴ represents -O-, -S-, -SO₂-, -NR⁷⁶CO-, -NR⁷⁷SO₂- or -NR⁷⁸- (wherein R⁷⁶, R⁷⁷ and R⁷⁸ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁸ is as defined hereinbefore); and

9) $R^{54}C_{1-3}$ alkylIX⁹R⁵⁵ (wherein R⁵⁴, R⁵⁵ and X⁹ are as defined hereinbefore);

may be prepared by reacting a compound of the formula IX:

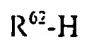
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15



(IX)

(wherein L¹, X¹, R¹, R², ring C, Z, n and s are as hereinbefore defined) with a compound of the
20 formula X:



(X)

(wherein R⁶² is as defined hereinbefore) to give a compound of the formula I or salt thereof.

The reaction may conveniently be effected in the presence of a base (as defined hereinbefore
25 in process (a)) and advantageously in the presence of an inert solvent or diluent (as defined
hereinbefore in process (a)), and at a temperature in the range, for example 0 to 150°C,
conveniently at about 50°C.

Process (a) is preferred over processes (b), (c) and (d).

(e) The production of those compounds of the formula I and salts thereof wherein one or
30 more of the substituents (R²)_m is represented by -NR⁷⁹R⁸⁰, where one (and the other is
hydrogen) or both of R⁷⁹ and R⁸⁰ are C₁₋₃alkyl, may be effected by the reaction of compounds

of formula I wherein the substituent (R^2)_m is an amino group and an alkylating agent, preferably in the presence of a base as defined hereinbefore. Such alkylating agents are C_{1-3} alkyl moieties bearing a displaceable moiety as defined hereinbefore such as C_{1-3} alkyl halides for example C_{1-3} alkyl chloride, bromide or iodide. The reaction is preferably effected

5 in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)) and at a temperature in the range, for example, 10 to 100°C, conveniently at about ambient temperature. The production of compounds of formula I and salts thereof wherein one or more of the substituents R^2 is an amino group may be effected by the reduction of a corresponding compound of formula I wherein the substituent(s) at the corresponding

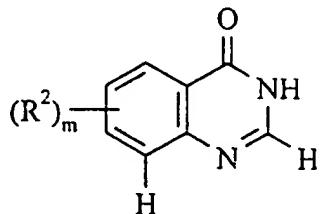
10 position(s) of the quinazoline group is/are a nitro group(s). The reduction may conveniently be effected as described in process (i) hereinafter. The production of a compound of formula I and salts thereof wherein the substituent(s) at the corresponding position(s) of the quinazoline group is/are a nitro group(s) may be effected by the processes described hereinbefore and hereinafter in processes (a-d) and (i-v) using a compound selected from the compounds of the

15 formulae (I-XXII) in which the substituent(s) at the corresponding position(s) of the quinazoline group is/are a nitro group(s).

(f) Compounds of the formula I and salts thereof wherein X^1 is $-SO-$ or $-SO_2-$ may be prepared by oxidation from the corresponding compound in which X^1 is $-S-$ or $-SO-$ (when X^1 is $-SO_2-$ is required in the final product). Conventional oxidation conditions and reagents for such reactions are well known to the skilled chemist.

Synthesis of Intermediates

(i) The compounds of formula III and salts thereof in which L^1 is halogeno may for example be prepared by halogenating a compound of the formula XI:



(XI)

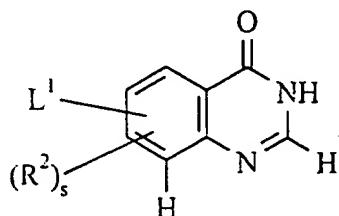
30 wherein R^2 and m are as hereinbefore defined).

Convenient halogenating agents include inorganic acid halides, for example thionyl chloride, phosphorus(III)chloride, phosphorus(V)oxygenchloride and phosphorus(V)chloride.

The halogenation reaction may be effected in the presence of an inert solvent or diluent such as for example a halogenated solvent such as methylene chloride, trichloromethane or carbon tetrachloride, or an aromatic hydrocarbon solvent such as benzene or toluene, or the reaction may be effected without the presence of a solvent. The reaction is conveniently effected at a 5 temperature in the range, for example 10 to 150°C, preferably in the range 40 to 100°C.

The compounds of formula XI and salts thereof may, for example, be prepared by reacting a compound of the formula XII:

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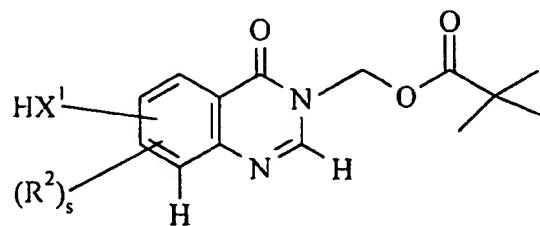


(XII)

15 (wherein R², s and L¹ are as hereinbefore defined) with a compound of the formula VIII as hereinbefore defined. The reaction may conveniently be effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)), advantageously at a temperature in the range, for example 10 to 150°C, conveniently at about 100°C.

20 Compounds of formula XI and salts thereof wherein at least one R² is R⁵X¹ and wherein X¹ is -O-, -S-, -SO-, -SO₂-, -CO-, -CONR⁷-, -SO₂NR⁸- or -NR¹⁰- (wherein R⁷, R⁸ and R¹⁰ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl), may for example also be prepared by the reaction of a compound of the formula XIII:

25



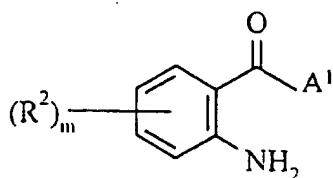
30

(XIII)

(wherein R² and s are as hereinbefore defined and X¹ is as hereinbefore defined in this section) with a compound of the formula VI as hereinbefore defined. The reaction may for example be effected as described for process (b) hereinbefore. The pivaloyloxymethyl group can then be cleaved by reacting the product with a base such as, for example, aqueous ammonia,

5 triethylamine in water, an alkali metal or alkaline earth metal hydroxide or alkoxide, preferably aqueous ammonia, aqueous sodium hydroxide or aqueous potassium hydroxide, in a polar protic solvent such as an alcohol, for example methanol or ethanol. The reaction is conveniently effected at a temperature in the range 20 to 100°C, preferably in the range 20 to 50°C.

10 The compounds of formula XI and salts thereof may also be prepared by cyclising a compound of the formula XIV:



15

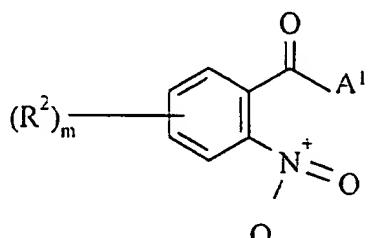
(XIV)

(wherein R² and m, are as hereinbefore defined, and A¹ is an hydroxy, alkoxy (preferably C₁-alkoxy) or amino group) whereby to form a compound of formula XI or salt thereof. The

20 cyclisation may be effected by reacting a compound of the formula XIV, where A¹ is an hydroxy or alkoxy group, with formamide or an equivalent thereof effective to cause cyclisation whereby a compound of formula XI or salt thereof is obtained, such as [3-(dimethylamino)-2-azaprop-2-enylidene]dimethylammonium chloride. The cyclisation is conveniently effected in the presence of formamide as solvent or in the presence of an inert 25 solvent or diluent such as an ether for example 1,4-dioxan. The cyclisation is conveniently effected at an elevated temperature, preferably in the range 80 to 200°C. The compounds of formula XI may also be prepared by cyclising a compound of the formula XIV, where A¹ is an amino group, with formic acid or an equivalent thereof effective to cause cyclisation whereby 30 a compound of formula XI or salt thereof is obtained. Equivalents of formic acid effective to cause cyclisation include for example a tri-C₁₋₄alkoxymethane, for example triethoxymethane and trimethoxymethane. The cyclisation is conveniently effected in the presence of a catalytic amount of an anhydrous acid, such as a sulphonic acid for example p-toluenesulphonic acid,

and in the presence of an inert solvent or diluent such as for example a halogenated solvent such as methylene chloride, trichloromethane or carbon tetrachloride, an ether such as diethyl ether or tetrahydrofuran, or an aromatic hydrocarbon solvent such as toluene. The cyclisation is conveniently effected at a temperature in the range, for example 10 to 100°C, preferably in
5 the range 20 to 50°C.

Compounds of formula XIV and salts thereof may for example be prepared by the reduction of the nitro group in a compound of the formula XV:



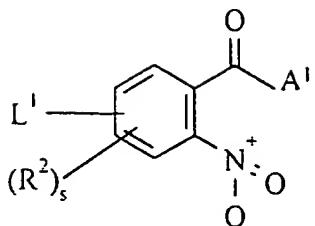
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(XV)

(wherein R², m and A¹ are as hereinbefore defined) to yield a compound of formula XIV as hereinbefore defined. The reduction of the nitro group may conveniently be effected by any of the procedures known for such a transformation. The reduction may be carried out, for
15 example, by stirring a solution of the nitro compound under hydrogen at 1 to 4 atmospheres pressure in the presence of an inert solvent or diluent as defined hereinbefore in the presence of a metal effective to catalyse hydrogenation reactions such as palladium or platinum. A further reducing agent is, for example, an activated metal such as activated iron (produced for example by washing iron powder with a dilute solution of an acid such as hydrochloric acid).
20 Thus, for example, the reduction may be effected by heating the nitro compound under hydrogen at 2 atmospheres pressure in the presence of the activated metal and a solvent or diluent such as a mixture of water and alcohol, for example methanol or ethanol, at a temperature in the range, for example 50 to 150°C, conveniently at about 70°C.

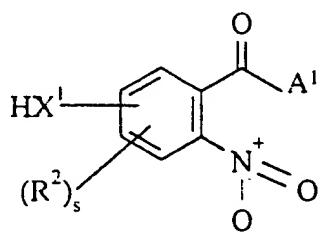
Compounds of the formula XV and salts thereof may for example be prepared by the
25 reaction of a compound of the formula XVI:

- 37 -



- 5 (wherein R², s, L' and A¹ are as hereinbefore defined) with a compound of the formula VIII as hereinbefore defined to give a compound of the formula XV. The reaction of the compounds of formulae XVI and VIII is conveniently effected under conditions as described for process (c) hereinbefore.

Compounds of formula XV and salts thereof wherein at least one R² is R⁵X¹ and
 10 wherein X¹ is -O-, -S-, -SO₂-, -CO-, -CONR⁷-, -SO₂NR⁸- or -NR¹⁰- (wherein R⁷, R⁸ and R¹⁰ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl), may for example also be prepared by the reaction of a compound of the formula XVII:



- 15 (XVII)

(wherein R², s and A¹ are as hereinbefore defined and X¹ is as hereinbefore defined in this section) with a compound of the formula VI as hereinbefore defined to yield a compound of formula XV as hereinbefore defined. The reaction of the compounds of formulae XVII and
 20 VI is conveniently effected under conditions as described for process (b) hereinbefore.

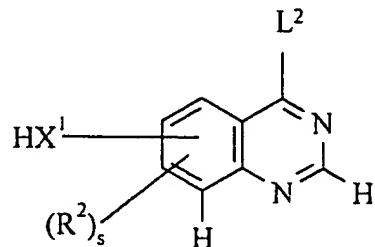
The compounds of formula III and salts thereof wherein at least one R² is R⁵X¹ and wherein X¹ is -CH₂- may be prepared for example as described above from a compound of the formula XV (in which R² is -CH₃) or XIII (in which HX¹ is -CH₃), by radical bromination or chlorination to give a -CH₂Br or -CH₂Cl group which may then be reacted with a compound 25 of the formula R⁵-H under standard conditions for such substitution reactions.

The compounds of formula III and salts thereof wherein at least one R² is R⁵X¹ and wherein X¹ is a direct bond may be prepared for example as described above from a compound of the formula XI, wherein the R⁵ group is already present in the intermediate compounds (for example in a compound of the formula XV) used to prepare the compound of formula XI.

The compounds of formula III and salts thereof wherein at least one R² is R⁵X¹ and wherein X¹ is -NR⁶CO- or -NR⁹SO₂- may be prepared for example from a compound of the formula XIII in which HX¹ is an -NHR⁶- or -NHR⁹- group (prepared for example from an amino group (later functionalised if necessary) by reduction of a nitro group) which is reacted with an acid chloride or sulfonyl chloride compound of the formula R⁵COCl or R⁵SO₂Cl.

The compounds of formula III and salts thereof wherein at least one R² is R⁵X¹ and wherein X¹ is -O-, -S-, -SO₂-, -OCO-, -CONR⁷-, -SO₂NR⁸- or -NR¹⁰- (wherein R⁷, R⁸ and R¹⁰ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl), may also be prepared for example by reacting a compound of the formula XVIII:

15



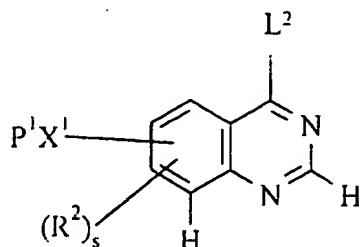
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(XVIII)

(wherein R² and s are as hereinbefore defined, X¹ is as hereinbefore defined in this section and L² represents a displaceable protecting moiety) with a compound of the formula VI as hereinbefore defined, whereby to obtain a compound of formula III in which L¹ is represented by L².

A compound of formula XVIII is conveniently used in which L² represents a phenoxy group which may if desired carry up to 5 substituents, preferably up to 2 substituents, selected from halogeno, nitro and cyano. The reaction may be conveniently effected under conditions as described for process (b) hereinbefore.

The compounds of formula XVIII and salts thereof may for example be prepared by deprotecting a compound of the formula XIX:



5

(XIX)

- (wherein R², s and L² are as hereinbefore defined, P¹ is a protecting group and X¹ is as hereinbefore defined in the section describing compounds of the formula XVIII). The choice 10 of protecting group P¹ is within the standard knowledge of an organic chemist, for example those included in standard texts such as "Protective Groups in Organic Synthesis" T.W. Greene and R.G.M.Wuts, 2nd Ed. Wiley 1991, including N-sulphonyl derivatives (for example, p-toluenesulphonyl), carbamates (for example, t-butyl carbonyl), N-alkyl derivatives (for example, 2-chloroethyl, benzyl) and amino acetal derivatives (for example 15 benzyloxymethyl). The removal of such a protecting group may be effected by any of the procedures known for such a transformation, including those reaction conditions indicated in standard texts such as that indicated hereinbefore, or by a related procedure. Deprotection may be effected by techniques well known in the literature, for example where P¹ represents a benzyl group deprotection may be effected by hydrogenolysis or by treatment with 20 trifluoroacetic acid.

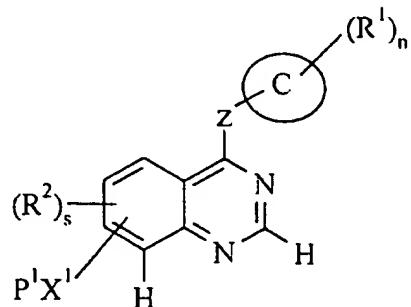
- One compound of formula III may if desired be converted into another compound of formula III in which the moiety L¹ is different. Thus for example a compound of formula III in which L¹ is other than halogeno, for example optionally substituted phenoxy, may be converted to a compound of formula III in which L¹ is halogeno by hydrolysis of a compound 25 of formula III (in which L¹ is other than halogeno) to yield a compound of formula XI as hereinbefore defined, followed by introduction of halide to the compound of formula XI, thus obtained as hereinbefore defined, to yield a compound of formula III in which L¹ represents halogen.

- (ii) Compounds of formula IV and salts thereof in which ring C is pyrazolyl may be prepared for example by reacting hydrazine with either a compound of the formula $R^2-C\equiv C-CO_2-C_{1,4}\text{alkyl}$, (Al-Jallo et al, J. Het. Chem. 1976, 13, 455), or a compound of the formula $R^2-C(O)-CH_2-C(O)-O-C_{1,4}\text{alkyl}$. In both cases the reaction may be effected by
- 5 heating the keto-ester compound in an inert diluent or solvent such as methanol, ethanol, isopropanol, isopentanol (preferably ethanol) in the presence of hydrazine hydrate. The reaction is effected at a temperature in a range 25-150°C preferably 50-100°C.

- (iii) Compounds of formula V as hereinbefore defined and salts thereof may be made by deprotecting the compound of formula XX:

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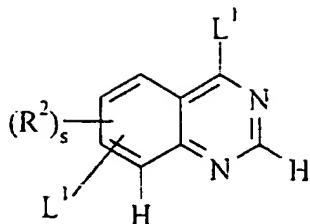
15



(XX)

- (wherein ring C, Z, R¹, R², P¹, n and s are as hereinbefore defined and X¹ is as hereinbefore defined in the section describing compounds of the formula V) by a process for example as described in (i) above.

- Compounds of the formula XX and salts thereof may be made by reacting compounds of the formulae XIX and IV as hereinbefore defined, under the conditions described in (a) hereinbefore, to give a compound of the formula XX or salt thereof.
- 25 (iv) Compounds of the formula VII and salts thereof may be made by reacting a compound of the formula XXI:



(XXI)

(wherein R^2 , s and each L^1 are as hereinbefore defined and the L^1 in the 4-position and the other L^1 in a further position on the quinazoline ring may be the same or different) with a compound of the formula IV as hereinbefore defined, the reaction for example being effected by a process as described in (a) above.

(v) Compounds of formula IX as defined hereinbefore and salts thereof may for example be made by the reaction of compounds of formula V as defined hereinbefore with compounds 15 of the formula XXII:



(wherein L^1 is as hereinbefore defined) to give compounds of formula IX or salts thereof. The 20 reaction may be effected for example by a process as described in (b) above.

(vi) Intermediate compounds wherein X^1 is $-SO-$ or $-SO_2-$ may be prepared by oxidation from the corresponding compound in which X^1 is $-S-$ or $-SO-$ (when X^1 is $-SO_2-$ is required in the final product). Conventional oxidation conditions and reagents for such reactions are well known to the skilled chemist.

25 When a pharmaceutically acceptable salt of a compound of the formula I is required, it may be obtained, for example, by reaction of said compound with, for example, an acid using a conventional procedure, the acid having a pharmaceutically acceptable anion.

Many of the intermediates defined herein, for example, those of the formulae V, VII, IX and XX are novel and these are provided as a further feature of the invention. The 30 preparation of these compounds is as described herein and/or is by methods well known to persons skilled in the art of organic chemistry.

The identification of compounds which potently inhibit the tyrosine kinase activity associated with VEGF receptors such as Flt and/or KDR and which inhibit angiogenesis and/or increased vascular permeability is desirable and is the subject of the present invention. These properties may be assessed, for example, using one or more of the procedures set out below:

5 (a) In Vitro Receptor Tyrosine Kinase Inhibition Test

This assay determines the ability of a test compound to inhibit tyrosine kinase activity. DNA encoding VEGF, FGF or EGF receptor cytoplasmic domains may be obtained by total gene synthesis (Edwards M, International Biotechnology Lab 5(3), 19-25, 1987) or by cloning. These may then be expressed in a suitable expression system to obtain polypeptide with tyrosine kinase activity. For example VEGF, FGF and EGF receptor cytoplasmic domains, which were obtained by expression of recombinant protein in insect cells, were found to display intrinsic tyrosine kinase activity. In the case of the VEGF receptor Flt (Genbank accession number X51602), a 1.7kb DNA fragment encoding most of the cytoplasmic domain, commencing with methionine 783 and including the termination codon, described by Shibuya et al (Oncogene, 1990, 5: 519-524), was isolated from cDNA and cloned into a baculovirus transplacement vector (for example pAcYM1 (see The Baculovirus Expression System: A Laboratory Guide. L.A. King and R. D. Possee, Chapman and Hall, 1992) or pAc360 or pBlueBacHis (available from Invitrogen Corporation)). This recombinant construct was co-transfected into insect cells (for example Spodoptera frugiperda 21(Sf21)) with viral DNA (eg Pharmingen BaculoGold) to prepare recombinant baculovirus. (Details of the methods for the assembly of recombinant DNA molecules and the preparation and use of recombinant baculovirus can be found in standard texts for example Sambrook et al, 1989, Molecular cloning - A Laboratory Manual, 2nd edition, Cold Spring Harbour Laboratory Press and O'Reilly et al, 1992, Baculovirus Expression Vectors - A Laboratory Manual, W. H. Freeman and Co, New York). For other tyrosine kinases for use in assays, cytoplasmic fragments starting from methionine 806 (KDR, Genbank accession number L04947), methionine 668 (EGF receptor, Genbank accession number X00588) and methionine 399 (FGF R1 receptor, Genbank accession number X51803) may be cloned and expressed in a similar manner.

For expression of cFlt tyrosine kinase activity, Sf21 cells were infected with plaque-pure cFlt recombinant virus at a multiplicity of infection of 3 and harvested 48 hours later.

Harvested cells were washed with ice cold phosphate buffered saline solution (PBS) (10mM sodium phosphate pH7.4, 138mM sodium chloride, 2.7mM potassium chloride) then resuspended in ice cold HNTG/PMSF (20mM Hepes pH7.5, 150mM sodium chloride, 10% v/v glycerol, 1% v/v Triton X100, 1.5mM magnesium chloride, 1mM ethylene glycol-
5 bis(βaminoethyl ether) N,N,N',N'-tetraacetic acid (EGTA), 1mM PMSF (phenylmethylsulphonyl fluoride); the PMSF is added just before use from a freshly-prepared 100mM solution in methanol) using 1ml HNTG/PMSF per 10 million cells. The suspension was centrifuged for 10 minutes at 13,000 rpm at 4°C, the supernatant (enzyme stock) was removed and stored in aliquots at -70°C. Each new batch of stock enzyme was titrated in the
10 assay by dilution with enzyme diluent (100mM Hepes pH 7.4, 0.2mM sodium orthovanadate, 0.1% v/v Triton X100, 0.2mM dithiothreitol). For a typical batch, stock enzyme is diluted 1 in 2000 with enzyme diluent and 50µl of dilute enzyme is used for each assay well.

A stock of substrate solution was prepared from a random copolymer containing tyrosine, for example Poly (Glu, Ala, Tyr) 6:3:1 (Sigma P3899), stored as 1 mg/ml stock in
15 PBS at -20°C and diluted 1 in 500 with PBS for plate coating.

On the day before the assay 100µl of diluted substrate solution was dispensed into all wells of assay plates (Nunc maxisorp 96-well immunoplates) which were sealed and left overnight at 4°C.

On the day of the assay the substrate solution was discarded and the assay plate wells
20 were washed once with PBST (PBS containing 0.05% v/v Tween 20) and once with 50mM Hepes pH7.4.

Test compounds were diluted with 10% dimethylsulphoxide (DMSO) and 25µl of diluted compound was transferred to wells in the washed assay plates. "Total" control wells contained 10% DMSO instead of compound. Twenty five microlitres of 40mM manganese(II)chloride containing 8µM adenosine-5'-triphosphate (ATP) was added to all test wells except "blank" control wells which contained manganese(II)chloride without ATP. To start the reactions 50µl of freshly diluted enzyme was added to each well and the plates were incubated at room temperature for 20 minutes. The liquid was then discarded and the wells were washed twice with PBST. One hundred microlitres of mouse IgG anti-phosphotyrosine antibody (Upstate Biotechnology Inc. product 05-321), diluted 1 in 6000 with PBST containing 0.5% w/v bovine serum albumin (BSA), was added to each well and the plates were incubated for 1 hour at room temperature before discarding the liquid and washing the

wells twice with PBST. One hundred microlitres of horse radish peroxidase (HRP)-linked sheep anti-mouse Ig antibody (Amersham product NXA 931), diluted 1 in 500 with PBST containing 0.5% w/v BSA, was added and the plates were incubated for 1 hour at room temperature before discarding the liquid and washing the wells twice with PBST. One 5 hundred microlitres of 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) solution, freshly prepared using one 50mg ABTS tablet (Boehringer 1204 521) in 50ml freshly prepared 50mM phosphate-citrate buffer pH5.0 + 0.03% sodium perborate (made with 1 phosphate citrate buffer with sodium perborate (PCSB) capsule (Sigma P4922) per 100ml distilled water), was added to each well. Plates were then incubated for 20-60 minutes at 10 room temperature until the optical density value of the "total" control wells, measured at 405nm using a plate reading spectrophotometer, was approximately 1.0. "Blank" (no ATP) and "total" (no compound) control values were used to determine the dilution range of test compound which gave 50% inhibition of enzyme activity.

15 (b) In Vitro HUVEC Proliferation Assay

This assay determines the ability of a test compound to inhibit the growth factor-stimulated proliferation of human umbilical vein endothelial cells (HUVEC).

HUVEC cells were isolated in MCDB 131 (Gibco BRL) + 7.5% v/v foetal calf serum (FCS) and were plated out (at passage 2 to 8), in MCDB 131 + 2% v/v FCS + 3 μ g/ml 20 heparin + 1 μ g/ml hydrocortisone, at a concentration of 1000 cells/well in 96 well plates. After a minimum of 4 hours they were dosed with the appropriate growth factor (i.e. VEGF 3ng/ml, EGF 3ng/ml or b-FGF 0.3ng/ml) and compound. The cultures were then incubated for 4 days at 37°C with 7.5% CO₂. On day 4 the cultures were pulsed with 1 μ Ci/well of tritiated-thymidine (Amersham product TRA 61) and incubated for 4 hours. The cells were 25 harvested using a 96-well plate harvester (Tomtek) and then assayed for incorporation of tritium with a Beta plate counter. Incorporation of radioactivity into cells, expressed as cpm, was used to measure inhibition of growth factor-stimulated cell proliferation by compounds.

(c) In Vivo Rat Uterine Oedema Assay

30 This test measures the capacity of compounds to reduce the acute increase in uterine weight in rats which occurs in the first 4-6 hours following oestrogen stimulation. This early increase in uterine weight has long been known to be due to oedema caused by increased

permeability of the uterine vasculature and recently Cullinan-Bove and Koos (Endocrinology, 1993, 133:829-837) demonstrated a close temporal relationship with increased expression of VEGF mRNA in the uterus. We have found that prior treatment of the rats with a neutralising monoclonal antibody to VEGF significantly reduces the acute increase in uterine weight,
5 confirming that the increase in weight is substantially mediated by VEGF.

Groups of 20 to 22-day old rats were treated with a single subcutaneous dose of oestradiol benzoate ($2.5\mu\text{g}/\text{rat}$) in a solvent, or solvent only. The latter served as unstimulated controls. Test compounds were orally administered at various times prior to the administration of oestradiol benzoate. Five hours after the administration of oestradiol
10 benzoate the rats were humanely sacrificed and their uteri were dissected, blotted and weighed. The increase in uterine weight in groups treated with test compound and oestradiol benzoate and with oestradiol benzoate alone was compared using a Student T test. Inhibition of the effect of oestradiol benzoate was considered significant when $p<0.05$.

According to a further aspect of the invention there is provided a pharmaceutical
15 composition which comprises a compound of the formula I as defined hereinbefore or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular,
20 intravascular or infusion) for example as a sterile solution, suspension or emulsion, for topical administration for example as an ointment or cream or for rectal administration for example as a suppository. In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compositions of the present invention are advantageously presented in unit dosage
25 form. The compound will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000mg per square metre body area of the animal, i.e. approximately 0.1-100mg/kg. A unit dose in the range, for example, 1-100mg/kg, preferably 1-50mg/kg is envisaged and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250mg of active ingredient.

30 According to a further aspect of the present invention there is provided a compound of the formula I or a pharmaceutically acceptable salt thereof as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

We have found that compounds of the present invention inhibit VEGF receptor tyrosine kinase activity and are therefore of interest for their antiangiogenic effects and/or their ability to cause a reduction in vascular permeability.

A further feature of the present invention is a compound of formula I, or a pharmaceutically acceptable salt thereof, for use as a medicament, conveniently a compound of formula I, or a pharmaceutically acceptable salt thereof, for use as a medicament for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human being.

According to a further feature of the invention there is provided a method for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof as defined hereinbefore.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. Preferably a daily dose in the range of 1-50mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

The antiangiogenic and/or vascular permeability reducing treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to the antiangiogenic and/or vascular permeability reducing treatment defined hereinbefore may be:

surgery, radiotherapy or chemotherapy. Such chemotherapy may cover three main categories of therapeutic agent:

(i) other antiangiogenic agents that work by different mechanisms from those defined hereinbefore (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function, angiostatin, razoxin,

5 thalidomide);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene, iodoxyfene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrozole, vorazole, exemestane), antiprogestogens, antiandrogens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and

10 antagonists (for example goserelin acetate, luprolide), inhibitors of testosterone 5 α -dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function. (such growth factors include for example platelet derived growth factor and hepatocyte growth factor such inhibitors include

15 growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors); and

(iii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example antifolates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside);

20 antitumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotapec); antimitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere);

25 topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan).

As stated above the compounds defined in the present invention are of interest for their antiangiogenic and/or vascular permeability reducing effects. Such compounds of the invention are expected to be useful in a wide range of disease states including cancer,

30 diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, excessive scar formation and adhesions, endometriosis, dysfunctional uterine bleeding and

ocular diseases with retinal vessel proliferation. In particular such compounds of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, breast, prostate, lungs and skin. More particularly such compounds of the invention are expected to inhibit the growth of those primary and recurrent solid tumours which are associated with VEGF, especially those tumours which are significantly dependent on VEGF for their growth and spread, including for example, certain tumours of the colon, breast, prostate, lung, vulva and skin.

In addition to their use in therapeutic medicine, the compounds of formula I and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of in vitro and in vivo test systems for the evaluation of the effects of inhibitors of VEGF receptor tyrosine kinase activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

It is to be understood that where the term "ether" is used anywhere in this specification it refers to diethyl ether.

The invention will now be illustrated in the following non-limiting Examples in which, unless otherwise stated:-

- (i) evaporation were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;
- (ii) operations were carried out at ambient temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon;
- (iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany;
- (iv) yields are given for illustration only and are not necessarily the maximum attainable;
- (v) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus, an oil-bath apparatus or a Kofler hot plate apparatus.
- (vi) the structures of the end-products of the formula I were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet;

(vii) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis;

(viii) petroleum ether refers to that fraction boiling between 40-60°C

5 (ix) the following abbreviations have been used:-

DMF N,N-dimethylformamide

DMSO dimethylsulphoxide

TFA trifluoroacetic acid

10 NMP 1-methyl-2-pyrrolidinone

THF tetrahydrofuran

HPLC RT retention time

Example 1

15 3-Phenyl-4,5-dihydro-1*H*-pyrazol-5-one (160mg, 1mmol). (*J. Org. Chem.*, 1967, 32, 3321-3324), was added in portions over 10 minutes to a suspension of sodium hydride (40mg, 1mmol, prewashed with THF) in DMF (3ml) under nitrogen. After stirring for 20 minutes at ambient temperature 4-chloro-6,7-dimethoxyquinazoline (112mg, 0.5mmol) was added and the mixture was heated for 20 minutes at 60°C. After cooling, the mixture was diluted with
20 saturated aqueous ammonium chloride solution and partitioned between ethyl acetate and water. The organic layer was washed with water, brine, dried ($MgSO_4$) and the volatiles removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (95/5 followed by 90/10). The volatiles were removed by evaporation, the residual solid was dissolved in methylene chloride and 3M ethereal hydrogen
25 chloride (1ml) was added. After removal of the solvent by evaporation, the residue was triturated with ether, collected by filtration and dried under vacuum to give 6,7-dimethoxy-4-(5-phenylpyrazol-3-yloxy)quinazoline (145mg, 75%).

¹H NMR Spectrum: (DMSOd₆; CF₃COOD) 3.98(s, 3H); 3.99(s, 3H); 6.66(s, 1H); 7.33(t, 1H); 7.43(t, 2H); 7.45(s, 1H); 7.62(s, 1H); 7.73(d, 1H); 8.9(s, 1H)

30 MS - ESI: 349 [MH]⁺

The starting material was prepared as follows:

A mixture of 4,5-dimethoxyanthranilic acid (19.7g) and formamide (10ml) was stirred and heated at 190°C for 5 hours. The mixture was allowed to cool to approximately 80°C and water (50ml) was added. The mixture was then allowed to stand at ambient temperature for 3 hours. The precipitate was collected by filtration, washed with water and dried to give 6,7-dimethoxy-3,4-dihydroquinazolin-4-one (3.65g).

To a portion (2.06g) of the material so obtained were added thionyl chloride (20ml) and DMF (1 drop) and the mixture stirred and heated at reflux for 2 hours. Excess thionyl chloride was removed by evaporation and the residue was partitioned between ethyl acetate and a saturated aqueous sodium hydrogen carbonate solution. The organic phase was washed with water, dried (MgSO_4) and the solvent removed by evaporation. The residue was purified by column chromatography using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent to give 4-chloro-6,7-dimethoxyquinazoline (0.6g, 27%).

Example 2

3-Benzyl-4,5-dihydro-1*H*-pyrazol-5-one (174mg, 1mmol), (J. Chem. Soc. Perk. Trans 1, 1980, 1618-1621), was added to a suspension of sodium hydride (40mg, 1mmol, prewashed with pentane) in DMF (3ml) under nitrogen. After stirring for 30 minutes at ambient temperature, 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (135mg, 0.4mmol) was added and the mixture was heated at 80°C for 1 hour. After cooling, the mixture was diluted with saturated aqueous ammonium chloride solution and partitioned between ethyl acetate and water. The precipitate was collected by filtration, washed with water, followed by ethanol, ether and dried under vacuum to give 4-(5-benzylpyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (150mg, 79%).

^1H NMR Spectrum: (DMSO $_d_6$; CF_3COOD) 2.35-2.45(m, 2H); 3.15-3.3(m, 2H); 3.45(t, 2H); 3.65(d, 2H); 3.75(t, 2H); 4.10(s, 3H); 4.11(s, 2H); 4.15(d, 2H); 4.45(d, 2H); 6.12(s, 1H); 7.3-7.5(m, 5H); 7.58(s, 1H); 7.75(s, 1H); 9.05(s, 1H)

MS - ESI: 476 [MH] $^+$

The starting material was prepared as follows:

A mixture of 4-hydroxy-3-methoxybenzoic acid (4.5g, 26.8mmol), 3-morpholinopropyl chloride (9.5g, 58.0mmol), (prepared according to J. Am. Chem. Soc. 1945, 67, 736), potassium carbonate (8.0g, 58mmol), potassium iodide (1.0g, 0.22mmol) and DMF (80ml) was stirred and heated at 100°C for 3 hours. The solid was removed by filtration

and the volatiles were removed by evaporation. The residue was dissolved in ethanol (50ml), 2M sodium hydroxide (50ml) was added and the mixture heated at 90°C for 2 hours. After partial evaporation, the mixture was acidified with concentrated hydrochloric acid, washed with ether and then subjected to purification on a Diaion (trade mark of Mitsubishi) HP20SS resin column, eluting with water and then with a gradient of methanol (0 to 25%) in hydrochloric acid (pH2). Partial evaporation of the solvents and lyophilisation gave 3-methoxy-4-(3-morpholinopropoxy)benzoic acid (8.65g, 97%).

¹H NMR Spectrum: (DMSO_d₆; TFA) 2.17-2.24(m, 2H); 3.10-3.16(m, 2H); 3.30(t, 2H); 3.52(d, 2H); 3.71(t, 2H); 3.82(s, 3H); 4.01(br d, 2H); 4.14(t, 2H); 7.08(d, 1H); 7.48(d, 1H);

10 7.59(dd, 1H)

MS - ESI: 296 [MH]⁺

Fuming nitric acid (1.5ml, 36.2mmol) was added slowly at 0°C to a solution of 3-methoxy-4-(3-morpholinopropoxy)benzoic acid (7.78g, 23.5mmol) in TFA (25ml). The cooling bath was removed and the reaction mixture stirred at ambient temperature for 1 hour.

15 The TFA was removed by evaporation and ice was added to the residue. The precipitate was collected by filtration, washed with a minimum of water followed by toluene and ether. The solid was dried under vacuum over phosphorus pentoxide to give 5-methoxy-4-(3-morpholinopropoxy)-2-nitrobenzoic acid (7.54g) which was used without further purification.

¹H NMR Spectrum: (DMSO_d₆; TFA) 2.16-2.23(m, 2H); 3.10-3.17(m, 2H); 3.30(t, 2H);

20 3.52(d, 2H); 3.66(t, 2H); 3.93(s, 3H); 4.02(br d, 2H); 4.23(t, 2H); 7.34(s, 1H); 7.61(s, 1H)

MS - EI: 340 [M]⁺

Thionyl chloride (15ml) and DMF (0.05ml) were added to 5-methoxy-4-(3-morpholinopropoxy)-2-nitrobenzoic acid (7.54g). The mixture was heated at 50°C for 1 hour, the excess thionyl chloride was removed by evaporation and by azeotroping with toluene (x2).

25 The resulting solid was suspended in THF (200ml) and ammonia was bubbled through the mixture for 30 minutes. The precipitate was removed by filtration and washed with THF. After concentration of the filtrate by evaporation, the product crystallised and was collected by filtration to give 5-methoxy-4-(3-morpholinopropoxy)-2-nitrobenzamide (5.25g) as light yellow crystals which were used without further purification.

30 ¹H NMR Spectrum: (DMSO_d₆; TFA) 2.17-2.24(m, 2H); 3.11-3.18(m, 2H); 3.31(t, 2H); 3.53(d, 2H); 3.67(t, 2H); 3.93(s, 3H); 4.03(br d, 2H); 4.21(t, 2H); 7.17(s, 1H); 7.62(s, 1H)

MS - EI: 339 [M]⁺

Concentrated hydrochloric acid (30ml) was added to a suspension of 5-methoxy-4-(3-morpholinopropoxy)-2-nitrobenzamide (5.67g) in methanol (150ml) and the mixture was heated to 60°C. When the 5-methoxy-4-(3-morpholinopropoxy)-2-nitrobenzamide had dissolved, iron powder (5.6g, 100mmol) was added in portions to the reaction mixture which was then heated for 90 minutes. After cooling, the insolubles were removed by filtration through diatomaceous earth, the volatiles were removed from the filtrate by evaporation and the residue was purified on a Diaion (trade mark of Mitsubishi) HP20SS resin column, eluting with water and then with hydrochloric acid (pH2). Concentration of the fractions by evaporation gave a precipitate which was collected by filtration and dried under vacuum over phosphorus pentoxide to give 2-amino-5-methoxy-4-(3-morpholinopropoxy)benzamide as a hydrochloride salt (4.67g, 75%) as beige crystals.

¹H NMR Spectrum: (DMSO_d₆; TFA) 2.22-2.28(m, 2H); 3.12(br t, 2H); 3.29(t, 2H); 3.51(d, 2H); 3.75(t, 2H); 3.87(s, 3H); 4.00(br d, 2H); 4.12(t, 2H); 7.06(s, 1H); 7.53(s, 1H)
MS - EI: 309 [M]⁺

A mixture of 2-amino-5-methoxy-4-(3-morpholinopropoxy)benzamide (4.57g, 12.25mmol) and Gold's reagent (2.6g, 15.89mmol) in dioxane (35ml) was heated at reflux for 5 hours. Acetic acid (0.55ml) and sodium acetate (1.0g) were added to the reaction mixture which was heated for a futher 3 hours. The mixture was cooled to ambient temperature and the volatiles removed by evaporation. The residue was adjusted to pH7 with 2M sodium hydroxide and then purified on a Diaion (trade mark of Mitsubishi) HP20SS resin column, eluting with methanol (gradient of 0 to 60%) in water. Concentration of the fractions by evaporation gave a precipitate which was collected by filtration and dried under vacuum over phosphorus pentoxide to give 4-hydroxy-6-methoxy-7-(3-morpholinopropoxy)quinazoline (3.04g, 78%) as a white solid.

¹H NMR Spectrum: (CDCl₃) 2.10(q, 2H); 2.48(m, 4H); 2.56(t, 2H); 3.72(t, 4H); 4.00(s, 3H); 4.24(t, 2H); 7.18(s, 1H); 7.60(s, 1H); 8.00(s, 1H); 10.86(br s, 1H)
MS - EI: 319 [M]⁺

A mixture of 4-hydroxy-6-methoxy-7-(3-morpholinopropoxy)quinazoline (638mg, 2mmol) and thionyl chloride (8ml) was heated at reflux for 30 minutes. Excess thionyl chloride was removed by evaporation and by azeotroping with toluene (x2). The residue was suspended in methylene chloride and 10% aqueous solution of sodium hydrogen carbonate was added to the mixture. The organic layer was separated, dried (MgSO₄) and the solvent

removed by evaporation. The residue was triturated with ether, the solid was collected by filtration, washed with ether and dried under vacuum to give 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (590mg, 87%).

¹H NMR Spectrum: (CDCl₃) 2.10-2.16(m, 2H); 2.48(br s, 4H); 2.57(t, 2H); 3.73(t, 4H);

5 4.05(s, 3H); 4.29(t, 2H); 7.36(s, 1H); 7.39(s, 1H); 8.86(s, 1H)

MS - ESI: 337 [MH]⁺

Example 3

Using an analogous procedure to that described for Example 2, 4-chloro-6-methoxy-7-

10 (3-morpholinopropoxy)quinazoline (169mg, 0.5mmol), (prepared as described for the starting material in Example 2), was reacted with 3-phenyl-4,5-dihydro-1*H*-pyrazol-5-one (200mg, 1.25mmol), (J. Org. Chem., 1967, 32, 3321-3324), in the presence of sodium hydride (50mg, 1.25mmol, prewashed with pentane) in DMF (3ml) to give 6-methoxy-7-(3-morpholinopropoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline as the free base. The free base
15 was dissolved in a mixture of methylene chloride/methanol (1/1) and 3M hydrochloric acid in methanol was added. The volatiles were removed by evaporation to give 6-methoxy-7-(3-morpholinopropoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline hydrochloride (115mg, 43%).

¹H NMR Spectrum: (DMSO_d₆; CF₃COOD) 2.3-2.4(m, 2H); 3.15(t, 2H); 3.3-3.4(m, 2H);

20 3.55(d, 2H); 3.75(t, 2H); 4.01(d, 2H); 4.05(s, 3H); 4.38(t, 2H); 6.7(s, 1H); 7.4(t, 1H); 7.5(t, 2H); 7.55(s, 1H); 7.7(s, 1H); 7.8(d, 2H); 8.91(s, 1H)

MS - EI: 461 [M.]⁺

Elemental analysis:

Found C 53.0 H 5.8 N 12.3

C₂₅H₂₂N₅O₄ 0.7H₂O 2HCl

Requires C 53.1 H 5.7 N 12.9%

25

Example 4

Using an analogous procedure to that described for Example 1, 4-chloro-6-methoxy-7-(2-methoxyethoxy)quinazoline (134mg, 0.5mmol) was reacted with 3-phenyl-4,5-dihydro-1*H*-pyrazol-5-one (160mg, 1mmol), (J. Org. Chem., 1967, 32, 3321-3324), in the presence of

30 sodium hydride (40mg, 1mmol, prewashed with THF) in DMF (3ml) to give 6-methoxy-7-(2-methoxyethoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline as the free base. The free base was dissolved in a mixture of methylene chloride/methanol (1/1) and 3M hydrochloric acid in

methanol was added. The volatiles were removed by evaporation to give 6-methoxy-7-(2-methoxyethoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline hydrochloride (155mg, 72%).

¹H NMR Spectrum: (DMSO_d₆; CF₃COOD) 3.38(s, 3H); 3.85(t, 2H); 4.09(s, 3H); 4.43(t, 2H); 6.74(s, 1H); 7.42(t, 1H); 7.51(t, 2H); 7.58(s, 1H); 7.76(s, 1H); 7.82(d, 2H); 9.15(s, 1H)

5 MS - EI: 392 [M.]^{*}

Elemental analysis:	Found	C 56.0 H 5.3 N 12.3
C ₂₁ H ₂₀ N ₄ O ₄ 1.6H ₂ O 0.75HCl	Requires	C 56.2 H 5.4 N 12.5%

The starting material was prepared as follows:

10 A mixture of ethyl 4-hydroxy-3-methoxybenzoate (9.8g, 50mmol), 2-bromoethyl methyl ether (8.46ml, 90mmol) and potassium carbonate (12.42g, 90mmol) in acetone (60ml) was heated at reflux for 30 hours. The mixture was allowed to cool and the solids removed by filtration. The volatiles were removed from the filtrate by evaporation and the residue triturated with hexane to give ethyl 3-methoxy-4-(2-methoxyethoxy)benzoate (11.3g, 89%) as
15 a white solid.

m.p. 57-60°C

¹H NMR Spectrum: (DMSO_d₆) 1.31(t, 3H); 3.29(s, 3H); 3.32(s, 3H); 3.68(m, 2H); 4.16(m, 2H); 4.28(q, 2H); 7.06(d, 1H); 7.45(d, 1H); 7.56(dd, 1H)

MS - FAB: 255 [MH]^{*}

20 Ethyl 3-methoxy-4-(2-methoxyethoxy)benzoate (9.5g, 37mmol) was added in portions to stirred concentrated nitric acid (75ml) at 0°C. The mixture was allowed to warm to ambient temperature and stirred for a further 90 minutes. The mixture was diluted with water and extracted with methylene chloride, dried (MgSO₄) and the solvent removed by evaporation. The residue was triturated with hexane to give ethyl 5-methoxy-4-(2-methoxyethoxy)-2-nitrobenzoate (10.6g, 95%) as an orange solid.
25

m.p. 68-69°C

¹H NMR Spectrum: (DMSO_d₆) 1.27(t, 3H); 3.30(s, 3H); 3.69(m, 2H); 3.92(s, 3H); 4.25(m, 2H); 4.29(q, 2H); 7.30(s, 1H); 7.65(s, 1H)

MS - Cl: 300 [MH]^{*}

30 A mixture of ethyl 5-methoxy-4-(2-methoxyethoxy)-2-nitrobenzoate (10.24g, 34mmol), cyclohexene (30ml) and 10% palladium-on-charcoal catalyst (2.0g) in methanol (150ml) was heated at reflux for 5 hours. The reaction mixture was allowed to cool and

diluted with methylene chloride. The catalyst was removed by filtration and the volatiles removed from the filtrate by evaporation. The residue was recrystallised from ethyl acetate/hexane to give ethyl 2-amino-5-methoxy-4-(2-methoxyethoxy) benzoate (8.0g) as a buff solid. Formamide (80ml) was added to this product and the mixture heated at 170°C for 5 18 hours. About half the solvent was removed by evaporation under high vacuum and the residue was left to stand overnight. The solid product was collected by filtration, washed with ether and dried to give 6-methoxy-7-(2-methoxyethoxy)-3,4-dihydroquinazolin-4-one (5.3g, 62% over two steps) as a grey solid.

¹H NMR Spectrum: (DMSO_d₆) 3.35(s, 3H); 3.74(m, 2H); 3.89(s, 3H); 4.26(m, 2H); 7.15(s,

10 1H); 7.47(s, 1H); 7.98(s, 1H); 12.03(br s, 1 H)

MS - CI: 251 [MH]⁺

DMF (0.5ml) was added to a mixture of 6-methoxy-7-(2-methoxyethoxy)-3,4-dihydroquinazolin-4-one (5.1g, 20mmol) in thionyl chloride (50ml). The mixture was stirred and heated at reflux for 3 hours, allowed to cool and the excess thionyl chloride removed by 15 evaporation. The residue was suspended in methylene chloride and washed with aqueous sodium hydrogen carbonate solution. The aqueous phase was extracted with methylene chloride and the combined extracts dried (MgSO₄). The crude product was recrystallised from methylene chloride/hexane to give 4-chloro-6-methoxy-7-(2-methoxyethoxy)quinazoline (2.8g, 51%) as a fine white solid.

20 ¹H NMR Spectrum: (DMSO_d₆) 3.37(s, 3H); 3.77(m, 2H); 4.01(s, 3H); 4.37(m, 2H); 7.40(s, 1H); 7.49(s, 1H); 8.88(s, 1H)

MS - CI: 269 [MH]⁺

Example 5

25 3-(4-Fluorophenyl)-4,5-dihydro-1*H*-pyrazol-5-one (222mg, 1.25mmol) was added in portions over 10 minutes to a suspension of sodium hydride (50mg, 1.25mmol, prewashed with hexane) in DMF (3ml) under nitrogen. After stirring for 20 minutes at ambient temperature, 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (169mg, 0.5mmol), (prepared as described for the starting material in Example 2), was added and the mixture was 30 heated at 60°C for 1 hour. After cooling, the mixture was diluted with aqueous ammonium chloride solution and ether was added. The precipitate was collected by filtration, washed with water, and dried under vacuum. The solid was dissolved in methylene chloride/methanol

(1/1) and 4M ethereal hydrogen chloride (0.5ml) was added. After removal of the solvent by evaporation, the solid was triturated with ether, collected by filtration and dried under vacuum to give 4-(5-(4-fluorophenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline hydrochloride (115mg, 48%).

5 ^1H NMR Spectrum: (DMSO_d₆; CF₃COOD) 2.3-2.4(m, 2H); 3.1-3.2(m, 2H); 3.35(t, 2H);
3.55(d, 2H); 3.75(t, 2H); 4.02(d, 2H); 4.04(s, 3H); 4.35(t, 2H); 6.71(s, 1H); 7.35(t, 2H);
7.53(s, 1H); 7.67(s, 1H); 7.83(dd, 2H); 8.86(s, 1H)
MS - ESI: 480 [MH]⁺

Elemental analysis: Found C 52.7 H 5.4 N 12.5
10 C₂₅H₂₆N₅O₄F 1.2H₂O 1.9HCl Requires C 52.6 H 5.3 N 12.3%

The starting material was prepared as follows:

To a solution of methyl 4-fluorobenzoyl acetate (588mg, 3mmol), (Clark, J.Chem. Soc. 1971, 1945) in ethanol (6ml) was added hydrazine hydrate (150mg, 3mmol). After 15 stirring for 30 minutes at ambient temperature, the mixture was stirred at 80°C for 30 minutes. After cooling, ether was added. The precipitate was collected by filtration, washed with ether and dried under vacuum to give 3-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-5-one (504mg, 94%).

19 ^1H NMR Spectrum: (DMSO_d₆; CF₃COOD) 6.2(d, 0.25H, enolic proton partly exchanged);
7.35(t, 2H); 7.8-7.9(m, 2H)
MS - EI: 178 [M.]⁺

Elemental analysis: Found C 60.8 H 4.0 N 15.9
C₉H₇N₂OF Requires C 60.8 H 4.0 N 15.7%

25 Example 6

3-Phenyl-4,5-dihydro-1*H*-pyrazol-5-one (270mg, 1.68 mmol), (J. Org. Chem., 1967, 32, 3321-3324), was added in portions over 10 minutes to a suspension of sodium hydride (70mg, 1.68mmol, prewashed with pentane) in DMF (3ml) under nitrogen. After stirring for 1 hour at ambient temperature 4-chloro-7-(2-methoxyethoxy)quinazoline (160mg, 0.67mmol) 30 was added and the mixture was heated for 1 hour at 60°C. After cooling, the mixture was diluted with saturated aqueous ammonium chloride solution and partitioned between ethyl acetate and water. The organic layer was washed with water, brine, dried (MgSO₄) and the

volatiles removed by evaporation. The residue was purified by column chromatography eluting with methanol/methylene chloride (5/95). The volatiles were removed by evaporation, the residual solid was dissolved in methylene chloride and 3M ethereal hydrogen chloride (0.5ml) was added. After removal of the solvent by evaporation, the residue was triturated 5 with ether, collected by filtration and dried under vacuum to give 7-(2-methoxyethoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline hydrochloride (120mg, 46%).

¹H NMR Spectrum: (DMSO_d₆; CF₃COOD) 3.36(s, 3H); 3.8(t, 2H); 4.4(t, 2H); 6.7(s, 1H); 7.4(t, 1H); 7.4-7.55(m, 4H); 7.8(d, 2H); 8.35(d, 1H); 8.94(s, 1H)

MS - ESI: 363 [MH]⁺

10 Elemental analysis: Found C 62.5 H 4.9 N 14.3
C₂₀H₁₈N₄O₃ 0.6HCl Requires C 62.2 H 4.9 N 14.5%

The starting material was prepared as follows:

A solution of 2-amino-4-fluorobenzoic acid (3g, 19.3mmol) in formamide (30ml) was 15 heated at 150°C for 6 hours. The reaction mixture was poured onto ice/water 1/1 (250ml). The precipitated solid was collected by filtration, washed with water and dried to give 7-fluoro-3,4-dihydroquinazolin-4-one (2.6g, 82%).

Sodium (400mg, 17mmol) was added carefully to 2-methoxyethanol (10ml) and the mixture heated at reflux for 30 minutes. 7-Fluoro-3,4-dihydroquinazolin-4-one (750mg, 20 4.57mmol) was added to the resulting solution and the mixture heated at reflux for 15 hours. The mixture was cooled and poured into water (250ml). The mixture was acidified to pH4 with concentrated hydrochloric acid. The resulting solid product was collected by filtration, washed with water and then with ether, and dried under vacuum to give 7-(2-methoxyethoxy)-3,4-dihydroquinazolin-4-one (580mg, 58%).

25 A solution of 7-(2-methoxyethoxy)-3,4-dihydroquinazolin-4-one (500mg, 2.2mmol) in thionyl chloride (15ml) and DMF (0.1ml) was heated at reflux for 3 hours. The volatiles were removed by evaporation to give 4-chloro-7-(2-methoxyethoxy)quinazoline hydrochloride as a cream solid (520mg, 83%).

30 A suspension of 4-chloro-7-(2-methoxyethoxy)quinazoline hydrochloride (500mg, 1.8mmol) in a mixture of water (20ml) and ethyl acetate (20ml) was diluted with a saturated solution of sodium hydrogen carbonate. After stirring at ambient temperature for 15 minutes

the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried (MgSO_4) and evaporated to give 4-chloro-7-(2-methoxyethoxy)quinazoline (345mg, 80%).

Example 7

5 Using an analogous procedure to that described for Example 6, 4-chloro-6-methoxy-7-(2-(imidazol-1-yl)ethoxy)quinazoline (0.2g, 0.66mmol) was reacted with 3-phenyl-4,5-dihydro-1*H*-pyrazol-5-one (260mg, 1.6mmol), (J. Org. Chem., 1967, 32, 3321-3324), in DMF (3ml) containing sodium hydride (65mg, 1.6mmol) to give, after purification, 7-(2-(imidazol-1-yl)ethoxy)-6-methoxy-4-(5-phenylpyrazol-3-yloxy)quinazoline hydrochloride (100mg, 10 28%).

'H NMR Spectrum: (DMSO_d₆; CF₃COOD) 4.05(s, 3H); 4.70(t, 2H); 4.79(t, 2H); 6.7(s, 1H); 7.4(t, 1H); 7.5(t, 2H); 7.57(s, 1H); 7.7(s, 1H); 7.73(s, 1H); 7.8(d, 1H); 7.85(s, 1H); 8.91(s, 1H); 9.22(s, 1H)

MS - ESI: 429 [MH]⁺

15 Elemental analysis: Found C 50.6 H 4.5 N 15.3
C₂₃H₂₀N₆O₃ 1.5H₂O 2.5HCl Requires C 50.5 H 4.7 N 15.4%

The starting material was prepared as follows:

A mixture of 2-amino-4-benzyloxy-5-methoxybenzamide (10g, 0.04mol), (prepared according to J. Med. Chem. 1977, vol 20, 146-149), and Gold's reagent (7.4g, 0.05mol) in 20 dioxane (100ml) was stirred and heated at reflux for 24 hours. Sodium acetate (3.02g, 0.037mol) and acetic acid (1.65ml, 0.029mol) were added to the reaction mixture and it was heated for a further 3 hours. The volatiles were removed by evaporation, water was added to the residue, the solid was collected by filtration, washed with water and dried. Recrystallisation from acetic acid gave 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (8.7g, 84%).

25 Sodium hydride (1.44g of a 60% suspension in mineral oil, 36mmol) was added in portions over 20 minutes to a solution of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (8.46g, 30mmol), in DMF (70ml) and the mixture was stirred for 1.5 hours. Chloromethyl pivalate (5.65g, 37.5mmol) was added dropwise and the mixture stirred for 2 hours at ambient temperature. The mixture was diluted with ethyl acetate (100ml) and poured onto ice/water (400ml) and 2M hydrochloric acid (4ml). The organic layer was separated and the aqueous layer extracted with ethyl acetate, the combined extracts were washed with brine, dried (MgSO_4) and the solvent removed by evaporation. The residue was triturated with a mixture of

ether and petroleum ether, the solid was collected by filtration and dried under vacuum to give 7-benzyloxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (10g, 84%).

¹H NMR Spectrum: (DMSO_d₆) 1.11(s, 9H); 3.89(s, 3H); 5.3(s, 2H); 5.9(s, 2H); 7.27(s, 1H); 7.35(m, 1H); 7.47(t, 2H); 7.49(d, 2H); 7.51(s, 1H); 8.34(s, 1H)

5 A mixture of 7-benzyloxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (7g, 17.7mmol) and 10% palladium-on-charcoal catalyst (700mg) in ethyl acetate (250ml), DMF (50ml), methanol (50ml) and acetic acid (0.7ml) was stirred under hydrogen at atmospheric pressure for 40 minutes. The catalyst was removed by filtration and the solvent removed from the filtrate by evaporation. The residue was triturated with ether, collected by
10 filtration and dried under vacuum to give 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (4.36g, 80%).

¹H NMR Spectrum: (DMSO_d₆) 1.1(s, 9H); 3.89(s, 3H); 5.89(s, 2H); 7.0(s, 1H); 7.48(s, 1H); 8.5(s, 1H)

15 Diethyl azodicarboxylate (435mg, 2.5mmol) was added dropwise to a suspension of 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (612mg, 2mmol), 2-(imidazol-1-yl)ethanol (280mg, 2.5mmol), (J. Med. Chem. 1993, 25, 4052-4060), and triphenylphosphine (655mg, 2.5mmol) in methylene chloride (10ml) at 5°C. The mixture was stirred for 10 minutes at 5°C and then 1 hour at ambient temperature. The mixture was poured directly on to a silica column and eluted with methylene chloride/methanol (95/5) to
20 give 7-(2-(imidazol-1-yl)ethoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (640mg, 80%).

¹H NMR Spectrum: (CDCl₃) 1.19(s, 9H); 3.98(s, 3H); 4.34(m, 2H); 4.45(m, 2H); 5.94(s, 2H); 7.02(s, 1H); 7.07(s, 1H); 7.11(s, 1H); 7.64(s, 1H); 7.67(s, 1H); 8.17(s, 1H)

MS - ESI: 423 [MNa]⁺

25 Elemental analysis: Found C 58.3 H 6.4 N 13.9
C₂₀H₂₄N₂O₅ 0.7H₂O Requires C 58.2 H 6.2 N 13.6%

A solution of 7-(2-(imidazol-1-yl)ethoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (640mg, 1.6mmol) in saturated methanolic ammonia (10ml) was stirred for 15 hours at ambient temperature. The volatiles were removed by evaporation, the

solid was triturated with ether, collected by filtration and dried under vacuum to give 7-(2-(imidazol-1-yl)ethoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (412mg, 90%).

¹H NMR Spectrum: (DMSO_d₆) 3.89(s, 3H); 4.4-4.5(m, 4H); 6.9(s, 1H); 7.16(s, 1H); 7.28(s, 1H); 7.47(s, 1H); 7.7(s, 1H); 7.99(s, 1H)

5 MS - ESI: 287 [MH]⁺

Elemental Analysis: Found C 57.8 H 5.2 N 19.3

C₁₄H₁₄N₄O₃ 0.3H₂O Requires C 57.7 H 5.1 N 19.2%

A mixture of 7-(2-(imidazol-1-yl)ethoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (412mg, 1.44mmol), thionyl chloride (5 ml) and DMF (0.2ml) was heated at reflux for 1 hour.

10 The mixture was diluted with toluene and the volatiles were removed by evaporation. The residue was suspended in methylene chloride, cooled to 0°C and aqueous sodium hydrogen carbonate solution was added. The resulting precipitate was collected by filtration and dried under vacuum to give 4-chloro-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline (258mg, 59%).

15 ¹H NMR Spectrum: (DMSO_d₆) 4.01(s, 3H); 4.47(m, 2H); 4.53(m, 2H); 6.89(s, 1H); 7.27(s, 1H); 7.41(s, 1H); 7.49(s, 1H); 7.70(s, 1H); 8.88(s, 1H)

MS - ESI: 327 [MNa]⁺

Example 8

20 Using an analogous procedure to that described for Example 6, 4-chloro-6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)quinazoline (156mg, 0.5mmol) was reacted with 3-phenyl-4,5-dihydro-1*H*-pyrazol-5-one (200mg, 1.25mmol), (*J. Org. Chem.*, 1967, 32, 3321-3324), in DMF (3ml) containing sodium hydride (50mg, 1.25mmol) to give, after purification, 6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline hydrochloride (180mg, 75%).

¹H NMR Spectrum: (DMSO_d₆; CF₃COOD) 3.27(s, 3H); 3.52(t, 2H); 3.68(t, 2H); 3.9(t, 2H); 4.04(s, 3H); 4.38(t, 2H); 6.72(s, 1H); 7.4(t, 1H); 7.48(t, 2H); 7.51(s, 1H); 7.67(s, 1H); 7.8(d, 2H); 8.9(s, 1H)

MS - ESI: 437 [MH]⁺

30 Elemental analysis: Found C 57.5 H 5.8 N 11.7

$C_{23}H_{24}N_4O_5$ 0.5H₂O 0.85HCl

Requires C 58.0 H 5.5 N 11.8%

The starting material was prepared as follows:

Diethyl azodicarboxylate (864μl, 5.5mmol) was added dropwise to a mixture of 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (1.2g, 3.9mmol) (prepared as described for the starting material in Example 7), triphenylphosphine (1.44g, 5.5mmol) and 2-(2-methoxyethoxy)ethanol (653μl, 5.5mmol) in methylene chloride (70ml) cooled at 0°C. The mixture was stirred for 1.5 hours at ambient temperature and the solvent was removed by evaporation. The residue was purified by column chromatography eluting with a mixture of ethyl acetate/methylene chloride (50/50 followed by 80/20). The purified solid was suspended in ether, collected by filtration and dried under vacuum to give 6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (1.70g, 100%).

¹H NMR Spectrum: (DMSOd₆) 1.13(s, 9H); 3.26(s, 3H); 3.5(m, 2H); 3.65(m, 2H); 3.85(m,

15 2H); 3.91(s, 3H); 4.3(m, 2H); 5.9(s, 2H); 7.2(s, 1H); 7.5(s, 1H); 8.4(s, 1H)

Saturated methanolic ammonia (20ml) was added to a solution of 6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (2.26g, 5.5mmol) in a mixture of ethanol (40ml) and methylene chloride (15ml). The mixture was stirred for 24 hours at ambient temperature, and further methanolic ammonia (20ml) was added. The mixture was stirred for a further 24 hours at ambient temperature and the volatiles were removed by evaporation. The residue was triturated with ether, collected by filtration, dried under vacuum to give 6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-3,4-dihydroquinazolin-4-one (975mg, 78%).

¹H NMR Spectrum: (DMSOd₆) 3.25(s, 3H); 3.45(t, 2H); 3.6(t, 2H); 3.8(t, 2H); 3.9(s, 3H);

25 4.2(t, 2H); 7.15(s, 1H); 7.45(s, 1H); 8.0(s, 1H)

MS - EI: 294 [M]⁺

A solution of 6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-3,4-dihydroquinazolin-4-one (930mg, 3.16mmol) in thionyl chloride (15ml) and DMF (150μl) was heated at 60°C for 1.5 hours. The mixture was allowed to cool and the volatiles were removed by evaporation and by azeotroping with toluene. The residue was dissolved in methylene chloride and 5% aqueous sodium hydrogen carbonate solution was added until the aqueous layer was at pH8. The organic layer was separated, washed with brine, dried (MgSO₄) and the solvent removed

by evaporation. The residue was purified by flash chromatography eluting with ethyl acetate to give 4-chloro-6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)quinazoline (863mg, 87%).
¹H NMR Spectrum: (DMSO-d₆) 3.24(s, 3H); 3.47(m, 2H); 3.62(m, 2H); 3.84(t, 2H); 4.01(s, 3H); 4.25(t, 2H); 7.41(s, 1H); 7.49(s, 1H); 8.88(s, 1H)

5

Example 9

Sodium hydride (40mg, 1mmol, prewashed with THF) was added to a suspension of 3-(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-5-one (220mg, 1mmol) in DMF (3ml) under nitrogen. After stirring for 20 minutes at ambient temperature, 4-chloro-6-methoxy-7-
10 (3-morpholinopropoxy)quinazoline (134mg, 0.4mmol), (prepared as described for the starting material in Example 2), was added and the mixture was heated for 30 minutes at 60°C. After cooling, the mixture was diluted with saturated aqueous ammonium chloride solution and partitioned between methylene chloride and water. The organic layer was washed with water, brine, dried (MgSO₄) and the volatiles were removed by evaporation. The residue was
15 purified by column chromatography eluting with methylene chloride/ethyl acetate/methanol (1/1/0 followed by 5/4/1). The volatiles were removed by evaporation and the residual solid was collected by filtration, washed with ether and dried under vacuum to give 4-(5-(3,4-dimethoxyphenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (120mg, 57%).
20 ¹H NMR Spectrum: (DMSO-d₆) 1.95-2.05(m, 2H); 2.4-2.6(m, 6H); 3.6(t, 4H); 3.81(s, 3H); 3.85(s, 3H); 4.02(s, 3H); 4.3(t, 2H); 6.65(s, 1H); 7.05(d, 1H); 7.35(d, 1H); 7.42(d, 2H); 7.55(s, 1H); 8.65(s, 1H)
MS - ESI: 522 [MH]⁺
Elemental analysis: Found C 61.5 H 6.1 N 13.0
25 C₂₁H₃₁N₅O₆ 0.2H₂O 0.12Et₂O Requires C 61.8 H 6.1 N 13.1%

The starting material was prepared as follows:

A solution of ethyl-3,4-dimethoxybenzoylacetate (1g, 4mmol), (Heterocycles 1979, 13, 239), in ethanol (5ml) containing hydrazine hydrate (192μl, 4mmol) was stirred for 30
30 minutes at ambient temperature followed by 40 minutes being heated at reflux. After cooling at ambient temperature, the mixture was concentrated to half the volume and ether (10ml) was

added. After trituration, the solid was collected by filtration, washed with ether and dried under vacuum to give 3-(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-5-one (521mg, 60%).
¹H NMR Spectrum: (DMSO_d₆) 3.76(s, 3H); 3.80(s, 3H); 5.81(s, 1H); 6.96(d, 1H); 7.18(dd, 1H); 7.25(d, 1H)

5 MS - ESI: 221 [MH]⁺

Example 10

Using an analogous procedure to that described in Example 9, 4-chloro-6-methoxy-7-(2-methoxyethoxy)quinazoline (134mg, 0.5mmol). (prepared as described for the starting material in Example 4), was reacted with 3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-5-one (190mg, 1mmol) in the presence of sodium hydride (40mg, 1mmol, prewashed with THF) in DMF (3ml) to give 6-methoxy-7-(2-methoxyethoxy)-4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)quinazoline (125mg, 59%).

¹H NMR Spectrum: (DMSO_d₆) 3.36(s, 3H); 3.8(t, 2H); 3.82(s, 3H); 4.01(s, 3H); 4.35(t, 2H); 6.6(s, 1H); 7.05(d, 2H); 7.45(s, 1H); 7.55(s, 1H); 7.75(d, 2H); 8.65(s, 1H)
15 MS - ESI: 423 [MH]⁺

Elemental analysis:	Found	C 61.0	H 5.2	N 13.0
C ₂₂ H ₂₂ N ₄ O ₅ 0.5H ₂ O	Requires	C 61.2	H 5.4	N 13.0%

20 The starting material was prepared using an analogous procedure to that described for the synthesis of 3-(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-5-one in Example 9. Ethyl-4-methoxybenzoylacetate (1g, 4.5mmol) was reacted with hydrazine hydrate (218μl, 4.5mmol) to give 3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-5-one (570mg, 67%).

¹H NMR Spectrum: (DMSO_d₆) 3.77(s, 3H); 5.77(s, 1H); 6.96(d, 2H); 7.60(d, 2H)
25 MS - ESI: 191 [MH]⁺

Example 11

Using an analogous procedure to that described in Example 9, 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (134mg, 0.4mmol), (prepared as described for the starting material in Example 2), was reacted with 3-(3-pyridyl)-4,5-dihydro-1*H*-pyrazol-5-one (161mg, 1mmol) in the presence of sodium hydride (40mg, 1 mmol, prewashed with THF) in

- 64 -

DMF (3ml) to give 6-methoxy-7-(3-morpholinopropoxy)-4-(5-(3-pyridyl)pyrazol-3-yloxy)quinazoline (110mg, 59%).

¹H NMR Spectrum: (DMSO_d₆) 1.95-2.05(m, 2H); 2.4(br s, 4H); 2.5(t, 2H); 3.6(t, 4H); 4.02(s, 3H); 4.28(t, 2H); 6.85(s, 1H); 7.45(s, 1H); 7.55(m, 1H); 7.6(s, 1H); 8.3(d, 1H); 8.6(d, 1H);

5 8.65(s, 1H); 9.05(s, 1H)

MS - ESI: 463 [MH]⁺

Elemental analysis:	Found	C 62.2	H 5.7	N 18.0
C ₂₄ H ₂₆ N ₆ O ₄	Requires	C 62.3	H 5.7	N 18.2%

10 The starting material was prepared using an analogous procedure to that described in Example 9. Ethyl-2-(3-pyridylcarbonyl)acetate (1g, 5.18mmol) was treated with hydrazine hydrate (251μl, 5.2mmol) to give 3-(3-pyridyl)-4,5-dihydro-1*H*-pyrazol-5-one (413mg, 50%).

¹H NMR Spectrum: (DMSO_d₆) 6.0(br s, 1H); 7.4(m, 1H); 8.05(m, 1H); 8.5(d, 1H); 8.92(s, 1H); 9.7-10(br s, 1H)

15 MS (ESI): 162 [MH]⁺

Example 12

Using an analogous procedure to that described in Example 9, 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (140mg, 0.415mmol), (prepared as described for the 20 starting material in Example 2), was reacted with 3-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-5-one (202mg, 1.04mmol) in the presence of sodium hydride (41.5mg, 1.04mmol, prewashed with THF) in DMF (2.5ml) to give 4-(5-(4-chlorophenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (150mg, 73%).

¹H NMR Spectrum: (DMSO_d₆) 1.95-2.05(m, 2H); 2.4(br s, 4H); 2.5(t, 2H); 3.6(t, 4H); 4.0(s, 3H); 4.25(t, 2H); 6.76(s, 1H); 7.42(s, 1H); 7.55(s, 1H); 7.6(d, 2H); 7.85(d, 2H); 8.65(s, 1H)
25 MS (ESI): 496 [MH]⁺

The starting material was prepared using an analogous procedure to that described in Example 9. Ethyl-4-chlorobenzoyl acetate (734mg, 3.24mmol) was treated with hydrazine hydrate (157μl, 3.24mmol) to give 3-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-5-one (244mg, 39%).

¹H NMR Spectrum: (DMSO_d₆) 5.9(br s, 1H); 7.45(d, 2H); 7.7(d, 2H); 9.7-10(br s, 1H)

MS (ESI): 195 [MH]⁺

Example 13

- Using an analogous procedure to that described in Example 9, 4-chloro-6-methoxy-7-
 5 (3-morpholinopropoxy)quinazoline (200mg, 0.59mmol), (prepared as described for the
 starting material in Example 2), was reacted with 3-(4-pyridyl)-4,5-dihydro-1*H*-pyrazol-5-one
 (240mg, 1.5mmol) in the presence of sodium hydride (59mg, 1.5mmol, prewashed with THF)
 in DMF (3ml) to give 6-methoxy-7-(3-morpholinopropoxy)-4-(5-(4-pyridyl)pyrazol-3-
 yloxy)quinazoline (130mg, 48%).
 10 ¹H NMR Spectrum: (DMSO_d₆) 1.95-2.05(m, 2H); 2.4(br s, 4H); 2.45(t, 2H); 3.6(t, 4H); 4.0(s,
 3H); 4.25(t, 2H); 6.95(s, 1H); 7.4(s, 1H); 7.55(s, 1H); 7.8(d, 2H); 8.62(s, 1H); 8.68(d, 2H)
 MS (ESI): 463 [MH]⁺

Elemental analysis:	Found	C 61.2	H 5.9	N 17.8
C ₂₄ H ₂₆ N ₆ O ₄ 0.5H ₂ O	Requires	C 61.1	H 5.8	N 17.8 %

15

- The starting material was prepared using an analogous procedure to that described in
 Example 9. Ethyl isonicotinoyl acetate (1g, 5.2mmol) was treated with hydrazine hydrate
 (251μl, 5.2mmol) in ethanol (5ml) to give 3-(4-pyridyl)-4,5-dihydro-1*H*-pyrazol-5-one
 (714mg, 86%).
 20 ¹H NMR Spectrum: (DMSO_d₆) 5.9-6.2(br s, 1H); 7.63(d, 2H); 8.6(br s, 2H)
 MS (ESI): 162 [MH]⁺

Example 14

- 3-Phenyl-4,5-dihydro-1*H*-pyrazol-5-one (182mg, 1.14mmol), (J. Org. Chem., 1967,
 25 32, 3321-3324), was added in portions to a suspension of sodium hydride (46mg, 1.14mmol,
 prewashed with pentane) in DMF (3ml). After stirring for 30 minutes at ambient temperature,
 4-chloro-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline (200mg, 0.57mmol)
 was added. The mixture was stirred for 30 minutes at 60°C. After cooling, the mixture was
 diluted with saturated aqueous ammonium chloride solution and partitioned between ethyl
 30 acetate and water. The organic layer was passed through an ISOLUTE (trade mark of IST)
 SPE column. The column was thoroughly washed with methanol. The product was recovered
 from the column by washing with a mixture of 0.1M solution of ammonia in methylene

chloride/methanol (1/1). The volatiles were removed by evaporation and the solid was collected by filtration, washed with ether and dried under vacuum to give 6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline (206mg, 76%).

¹H NMR Spectrum: (DMSO_d₆; CF₃COOD) 2.3-2.4(m, 2H); 2.98(s, 3H); 3.3-3.6(m, 5H); 3.6-

5 4.0(m, 5H); 4.04(s, 3H); 4.38(t, 2H); 6.75(s, 1H); 7.42(s, 1H); 7.5(t, 2H); 7.55(s, 1H); 7.7(s, 1H); 7.85(d, 2H); 8.9(s, 1H)

MS (ESI): 475 [MH]⁺

The starting material was prepared as follows:

10 1-Bromo-3-chloropropane (0.97ml, 9.8mmol) was added to a solution of 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (2.5g, 8.17mmol), (prepared as described for the starting material in Example 7), in DMF (40ml) containing potassium carbonate (2.8g, 20mmol). The mixture was stirred overnight at ambient temperature and partitioned between ethyl acetate and water. The organic layer was washed with water, brine, dried (MgSO₄) and evaporated to give 7-(3-chloropropoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (3.10g, 100%).

¹H NMR Spectrum: (DMSO_d₆) 1.12(s, 9H); 2.15(t, 2H); 3.8(t, 2H); 3.9(s, 3H); 4.25(t, 2H); 5.9(s, 2H); 7.2(s, 1H); 7.5(s, 1H); 8.36(s, 1H)

MS (ESI): 383 [MH]⁺

20 A solution of 7-(3-chloropropoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (3g, 7.84mmol) in 1-methylpiperazine (30ml) was heated at 100°C for 1 hour. After cooling, the mixture was partitioned between saturated ammonium chloride and methylene chloride. The organic layer was washed with water, brine, dried (MgSO₄) and the volatiles were removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (95/5 followed by 90/10). The volatiles were removed by evaporation to give 6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (3.24g, 92%).

A solution of 6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (3.1g, 7mmol) in 5M ammonia in methanol (60ml) was stirred at ambient temperature overnight. The volatiles were removed by evaporation and the residue was triturated with ether, collected by filtration, washed with

ether and dried under vacuum to give 6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)-3,4-dihydroquinazolin-4-one (2.1g, 91%).

¹H NMR Spectrum: (DMSO_d₆) 1.9-2.0(m, 2H); 2.2(s, 3H); 2.2-2.5(m, 10 H); 3.85(s, 3H); 4.15(t, 2H); 7.1(s, 1H); 7.45(s, 1H); 7.95(s, 1H)

5 MS (ESI): 331 [MH]⁺

A solution of 6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)-3,4-dihydroquinazolin-4-one (2.05g, 6.2mmol) in thionyl chloride (30ml) containing DMF (500μl) was heated at reflux for 30 minutes. After cooling, the volatiles were removed by evaporation. The residue was partitioned between methylene chloride and saturated aqueous 10 sodium hydrogen carbonate and the aqueous layer was adjusted to pH8 with solid sodium hydrogen carbonate. The organic layer was washed with water, brine, dried ($MgSO_4$) and the volatiles were removed by evaporation. The residue was triturated with ether, collected by filtration, washed with ether and dried under vacuum to give 4-chloro-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline (1.4g, 65%).

15 ¹H NMR Spectrum: (DMSO_d₆) 2.1(m, 2H); 2.2(s, 3H); 2.3-2.5(m, 10 H); 4.05(s, 3H); 4.3(t, 2H); 7.4(s, 1H); 7.45(s, 1H); 8.88(s, 1H)

Example 15

A solution of 3-amino-5-(4-methoxyphenyl)-4*H*-pyrazole (74mg, 0.39mmol), 20 (Synthesis, 1984, 3, 276), in isopropanol (3.5ml) was added to 4-chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (110mg, 0.34mmol) followed by 5M hydrogen chloride in isopropanol (78μl, 0.39mmol) and the mixture was heated at reflux for 1.5 hours. After cooling to 5°C, the precipitate was collected by filtration washed with isopropanol, followed by ether and dried under vacuum at 60°C to give 4-(5-(4-methoxyphenyl)pyrazol-25 3-ylamino)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline hydrochloride (133mg, 72%).

¹H NMR Spectrum: (DMSO_d₆, CH₃COOD) 1.6-1.75(m, 2H); 2.05(d, 2H); 2.1-2.2(m, 1H); 2.75(s, 3H); 3.05(t, 2H); 3.5(d, 2H); 3.8(s, 3H); 4.02(s, 3H); 4.1(d, 2H); 7.06(d, 2H); 7.08(s, 1H); 7.2(s, 1H); 7.37(d, 2H); 8.15(s, 1H); 8.92(s, 1H)

30 MS - ESI: 475 [MH]⁺

HPLC RT = 2.5 minutes

The starting material was prepared as follows:

- A solution of di-tert-butyl dicarbonate (41.7g, 0.19mol) in ethyl acetate (75ml) was added in portions to a solution of ethyl 4-piperidinocarboxylate (30g, 0.19mol) in ethyl acetate (150ml) cooled at 5°C, while maintaining the temperature in the range 0-5°C. After stirring
5 for 48 hours at ambient temperature, the mixture was poured onto water (300ml). The organic layer was separated, washed successively with water (200ml), 0.1M aqueous hydrochloric acid (200ml), saturated sodium hydrogen carbonate (200ml) and brine (200ml), dried ($MgSO_4$), and the volatiles were removed by evaporation to give ethyl 4-(1-tert-butyloxycarbonylpiperidine)carboxylate (48g, 98%).
10 1H NMR Spectrum: ($CDCl_3$) 1.25(t, 3H); 1.45(s, 9H); 1.55-1.70(m, 2H); 1.8-2.0(d, 2H); 2.35-2.5(m, 1H); 2.7-2.95(t, 2H); 3.9-4.1(br s, 2H); 4.15 (q, 2H)

- A solution of 1M lithium aluminium hydride in THF (133ml, 0.133mol) was added in portions to a solution of ethyl 4-(1-tert-butyloxycarbonylpiperidine)carboxylate (48g, 0.19mol) in dry THF (180ml) cooled at 0°C. After stirring at 0°C for 2 hours. water (30ml)
15 was added followed by 2M sodium hydroxide (10ml). The precipitate was filtered through diatomaceous earth and washed with ethyl acetate. The filtrate was washed with water, brine, dried ($MgSO_4$) and the volatiles were removed by evaporation to give 4-hydroxymethyl-1-tert-butyloxycarbonylpiperidine (36.3g, 89%).
20 1H NMR Spectrum: ($CDCl_3$) 1.05-1.2(m, 2H); 1.35-1.55(m, 10H); 1.6-1.8(m, 2H); 2.6-2.8(t, 2H); 3.4-3.6(t, 2H); 4.0-4.2(br s, 2H)
MS (EI): 215 [M.]⁺

- 1,4-Diazabicyclo[2.2.2]octane (42.4g, 0.378mol) was added to a solution of 4-hydroxymethyl-1-tert-butyloxycarbonylpiperidine (52.5g, 0.244mol) in tert-butyl methyl ether (525ml). After stirring for 15 minutes at ambient temperature, the mixture was cooled to 5°C
25 and a solution of toluene sulphonyl chloride (62.8g, 0.33mmol) in tert-butyl methyl ether (525ml) was added in portions over 2 hours while maintaining the temperature at 0°C. After stirring for 1 hour at ambient temperature, petroleum ether (1l) was added. The precipitate was removed by filtration. The volatiles were removed by evaporation to give a solid. The solid was dissolved in ether and washed successively with 0.5M aqueous hydrochloric acid (2x500ml), water, saturated sodium hydrogen carbonate and brine, dried ($MgSO_4$) and the volatiles were removed by evaporation to give 4-(4-methylphenylsulphonyloxymethyl)-1-tert-butyloxycarbonylpiperidine (76.7g, 85%).
30

¹H NMR Spectrum: (CDCl₃) 1.0-1.2(m, 2H); 1.45(s, 9H); 1.65(d, 2H); 1.75-1.9(m, 2H); 2.45(s, 3H); 2.55-2.75(m, 2H); 3.85(d, 1H); 4.0-4.2(br s, 2H); 7.35(d, 2H); 7.8(d, 2H)
MS (ESI): 392 [MNa]⁺

4-(4-Methylphenylsulphonyloxymethyl)-1-tert-butyloxycarbonylpiperidine (40g, 0.11mol) was added to a suspension of ethyl 3-methoxy-4-hydroxybenzoate (19.6g, 0.1mol) and potassium carbonate (28g, 0.2mol) in dry DMF (200ml). After stirring at 95°C for 2.5 hours, the mixture was cooled to ambient temperature and partitioned between water and ethyl acetate/ether. The organic layer was washed with water, brine, dried (MgSO₄) and the volatiles were removed by evaporation. The resulting oil was crystallised from petroleum ether and the suspension was stored overnight (at 5°C). The solid was collected by filtration, washed with petroleum ether and dried under vacuum to give ethyl 3-methoxy-4-(1-tert-butyloxycarbonylpiperidin-4-ylmethoxy)benzoate (35g, 89%).

m.p. 81-83°C

¹H NMR Spectrum: (CDCl₃) 1.2-1.35(m, 2H); 1.4(t, 3H); 1.48(s, 9H); 1.8-1.9(d, 2H); 2.0-2.15(m, 2H); 2.75(t, 2H); 3.9(d, 2H); 3.95(s, 3H); 4.05-4.25(br s, 2H); 4.35(q, 2H); 6.85(d, 1H); 7.55(s, 1H); 7.65(d, 1H)

MS (ESI): 416 [MNa]⁺

Elemental analysis:	Found	C 63.4	H 8.0	N 3.5
C ₂₁ H ₃₁ NO ₆ 0.3H ₂ O	Requires	C 63.2	H 8.0	N 3.5%

Formaldehyde (12M, 37% in water, 35ml, 420mmol) was added to a solution of ethyl 3-methoxy-4-(1-tert-butyloxycarbonylpiperidin-4-ylmethoxy)benzoate (35g, 89mmol) in formic acid (35ml). After stirring at 95°C for 3 hours, the volatiles were removed by evaporation. The residue was dissolved in methylene chloride and 3M hydrogen chloride in ether (40ml, 120mmol) was added. After dilution with ether, the mixture was triturated until a solid was formed. The solid was collected by filtration, washed with ether and dried under vacuum overnight at 50°C to give ethyl 3-methoxy-4-(1-methylpiperidin-4-ylmethoxy)benzoate (30.6g. quant.).

¹H NMR Spectrum: (DMSO_d₆) 1.29(t, 3H); 1.5-1.7(m, 2H); 1.95(d, 2H); 2.0-2.15(br s, 1H); 2.72(s, 3H); 2.9-3.1(m, 2H); 3.35-3.5(br s, 2H); 3.85(s, 3H); 3.9-4.05(br s, 2H); 4.3(q, 2H); 7.1(d, 1H); 7.48(s, 1H); 7.6(d, 1H)

MS (ESI): 308 [MH]⁺

- A solution of ethyl 3-methoxy-4-(1-methylpiperidin-4-ylmethoxy)benzoate (30.6g, 89mmol) in methylene chloride (75ml) was cooled to 0-5°C. TFA (37.5ml) was added followed by the addition in portions over 15 minutes of a solution of fuming 24M nitric acid (7.42ml, 178mmol) in methylene chloride (15ml). After completion of the addition, the
5 solution was allowed to warm up and stirred at ambient temperature for 2 hours. The volatiles were removed under vacuum and the residue was dissolved in methylene chloride (50ml). The solution was cooled to 0-5°C and ether was added. The precipitate was collected by filtration, and dried under vacuum at 50°C. The solid was dissolved in methylene chloride (500ml) and 3M hydrogen chloride in ether (30ml) was added followed by ether (500ml).
10 The solid was collected by filtration and dried under vacuum at 50°C to give ethyl 3-methoxy-4-(1-methylpiperidin-4-ylmethoxy)-6-nitrobenzoate (28.4g, 82%).
¹H NMR Spectrum: (DMSO-d₆) 1.3(t, 3H); 1.45-1.65(m, 2H); 1.75-2.1(m, 3H); 2.75(s, 3H); 2.9-3.05(m, 2H); 3.4-3.5(d, 2H); 3.95(s, 3H); 4.05(d, 2H); 4.3(q, 2H); 7.32(s, 1H); 7.66(s, 1H)
MS (ESI): 353 [MH]⁺
15 A suspension of ethyl 3-methoxy-4-(1-methylpiperidin-4-ylmethoxy)-6-nitrobenzoate (3.89g, 10mmol) in methanol (80ml) containing 10% platinum on activated carbon (50% wet) (389mg) was hydrogenated at 1.8 atmospheres pressure until uptake of hydrogen ceased. The mixture was filtered and the volatiles were removed by evaporation. The residue was dissolved in water (30ml) and adjusted to pH10 with a saturated solution of sodium hydrogen carbonate. The mixture was diluted with ethyl acetate/ether (1/1) and the organic layer was separated. The aqueous layer was further extracted with ethyl acetate/ether and the organic layers were combined. The organic layers were washed with water, brine, dried (MgSO₄),
20 filtered and the volatiles were removed by evaporation. The resulting solid was triturated in a mixture of ether/petroleum ether, filtered, washed with petroleum ether and dried under
25 vacuum at 60°C to give ethyl 6-amino-3-methoxy-4-(1-methylpiperidin-4-ylmethoxy)benzoate (2.58g, 80%).
m.p. 111-112°C
¹H NMR Spectrum: (CDCl₃) 1.35(t, 3H); 1.4-1.5(m, 2H); 1.85(m, 3H); 1.95(t, 2H); 2.29(s, 3H); 2.9(d, 2H); 3.8(s, 3H); 3.85(d, 2H); 4.3(q, 2H); 5.55(br s, 2H); 6.13(s, 1H); 7.33(s, 1H)
30 MS (ESI): 323 [MH]⁺

Elemental analysis:	Found	C 62.8	H 8.5	N 8.3
C ₁₇ H ₂₆ N ₂ O ₄ 0.2H ₂ O	Requires	C 62.6	H 8.2	N 8.6%

A solution of ethyl 6-amino-3-methoxy-4-(1-methylpiperidin-4-ylmethoxy)benzoate (16.1g, 50mmol) in 2-methoxyethanol (160ml) containing formamidine acetate (5.2g, 50mmol) was heated at 115°C for 2 hours. Formamidine acetate (10.4g, 100mmol) was added in portions every 30 minutes during 4 hours. Heating was prolonged for 30 minutes after the last addition. After cooling, the volatiles were removed under vacuum. The solid was dissolved in ethanol (100ml) and methylene chloride (50ml). The precipitate was removed by filtration and the filtrate was concentrated to a final volume of 100ml. The suspension was cooled to 5°C and the solid was collected by filtration, washed with cold ethanol followed by ether and dried under vacuum overnight at 60°C to give 6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-3,4-dihydroquinazolin-4-one (12.7g, 70%).

¹H NMR Spectrum: (DMSO_d₆) 1.25-1.4(m, 2H); 1.75(d, 2H); 1.9(t, 1H); 1.9(s, 3H); 2.16(s, 2H); 2.8(d, 2H); 3.9(s, 3H); 4.0(d, 2H); 7.11(s, 1H); 7.44(s, 1H); 7.97(s, 1H)

MS (ESI): 304 [MH]⁺

A solution of 6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-3,4-dihydroquinazolin-4-one (2.8g, 9.24mmol) in thionyl chloride (28ml) containing DMF (280μl) was refluxed at 85°C for 1 hour. After cooling, the volatiles were removed by evaporation. The precipitate was triturated with ether, filtered, washed with ether and dried under vacuum. The solid was dissolved in methylene chloride and saturated aqueous sodium hydrogen carbonate was added. The organic layer was separated, washed with water, brine, dried (MgSO₄) and evaporated to give 4-chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (2.9g, 98%).

¹H NMR Spectrum: (DMSO_d₆) 1.3-1.5(m, 2H); 1.75-1.9(m, 3H); 2.0(t, 1H); 2.25(s, 3H); 2.85(d, 2H); 4.02(s, 3H); 4.12(d, 2H); 7.41(s, 1H); 7.46(s, 1H); 8.9(s, 1H)

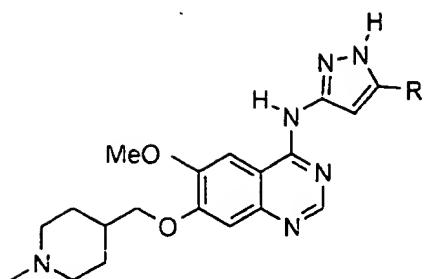
MS (ESI): 322 [MH]⁺

25

Examples 16-20

Using an analogous procedure to that described in Example 15, 4-chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (110 mg, 0.34 mol), (prepared as described for the starting material in Example 15), was reacted with the appropriate amino pyrazole to give, 30 as hydrochloride salts, the compounds described in Table 1 hereinafter.

Table 1



Example No.	Weight obtained mg	yield %	R	HPLC RT minutes	[MH] ⁺	Note
16	168	90	4-chlorophenyl	2.72	479	1
17	178	89	3,4-dichlorophenyl	2.99	514	2
18	145	80	4-methylphenyl	2.63	459	3
19	185	93	3-trifluoromethylphenyl	2.87	513.3	4
20	140	86	cyclopropyl	2.17	409.5	5

5 HPLC conditions: column: TSK gel Super ODS 2 mm; 4.6 mm x 5 cm; eluent: gradient 0-100% acetonitrile/water (1% acetic acid) over 7 minutes; column temperature 50°C; flow rate = 14 ml/minute; detection: UV at 254 nm.

Notes

- 1) 4-Chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline was reacted
10 with 3-amino-5-(4-chlorophenyl)-4H-pyrazole (76mg), (Synthesis, 1984, 3, 276), to give Example 16.
¹H NMR Spectrum: (DMSO_d₆, CD₃COOD) 1.55-1.75(m, 2H), 2.0-2.1(d, 2H), 2.15-2.25(m, 1H), 2.78(s, 3H), 3.05(t, 2H), 3.5(d, 2H), 4.0(s, 3H), 4.1(d, 2H), 7.29(s, 1H), 7.38(s, 1H), 7.58(d, 2H), 7.84(d, 2H), 8.3(s, 1H), 8.9(s, 1H)
- 15 2) 4-Chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline was reacted with 3-amino-5-(3,4-dichlorophenyl)-4H-pyrazole (89mg), (Synthesis, 1984, 3, 276), to give Example 17.

¹H NMR Spectrum: (DMSO_d₆, CD₃COOD) 1.55-1.7(m, 2H), 2.05(d, 2H), 2.15-2.25(m, 1H), 2.78(s, 3H), 3.02(t, 2H), 3.5(d, 2H), 4.01(s, 3H), 4.1(d, 2H), 7.36(s, 2H), 7.7-7.8(m, 2H), 8.11(s, 1H), 8.28(s, 1H), 8.92(s, 1H)

3) 4-Chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline was reacted
5 with 3-amino-5-(4-methylphenyl)-4*H*-pyrazole (68mg), (Synthesis, 1984, 3, 276), to give Example 18.

¹H NMR Spectrum: (DMSO_d₆, CD₃COOD) 1.55-1.7(m, 2H), 2.03(d, 2H), 2.1-2.2(m, 1H), 2.36(s, 3H), 2.77(s, 3H), 3.02(t, 2H), 3.5(d, 2H), 4.02(s, 3H), 4.10(d, 2H), 7.23(s, 1H), 7.32(d, 2H), 7.40(s, 1H), 7.70(d, 2H), 8.31(s, 1H), 8.9(s, 1H)

10 4) 4-Chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline was reacted with 3-amino-(3-trifluoromethylphenyl)-4*H*-pyrazole (89mg), (WO 98/25907), to give Example 19.

¹H NMR Spectrum: (DMSO_d₆, CD₃COOD) 1.6-1.7(m, 2H), 2.05(d, 2H), 2.15-2.25(m, 1H), 2.77(s, 3H), 3.05(t, 2H), 3.5(d, 2H), 4.0(s, 3H), 4.11(d, 2H), 7.42(d, 1H), 7.76(br s, 2H), 8.1(s, 1H), 8.19(s, 1H), 8.94(s, 1H)

15 5) 4-Chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline was reacted with 3-amino-5-cyclopropyl-4*H*-pyrazole (48mg) to give Example 20.

¹H NMR Spectrum: (DMSO_d₆, CD₃COOD) 0.7(d, 2H), 1.05(d, 2H), 1.6-1.8(m, 2H), 1.9-2.2(m, 3H), 2.8(s, 3H), 3.05(t, 2H), 3.5(d, 2H), 4.0(s, 3H), 4.1(d, 2H), 6.6(s, 1H), 7.4(s, 1H), 20 8.3(s, 1H), 8.9(s, 1H)

Example 21

A solution of 4-chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (161mg, 0.5mmol), (prepared as described for the starting material in Example 15), and 3-amino-5-phenyl-4*H*-pyrazole (91mg, 0.57mmol) in isopropanol (5ml) containing 5M hydrogen chloride in isopropanol (110μl, 0.55mmol) was heated at reflux for 1.5 hours. After cooling, the precipitate was collected by filtration and washed with isopropanol followed by ether. The solid was partitioned between aqueous sodium hydrogen carbonate and ethyl acetate. The organic layer was separated, washed with water, brine, dried (MgSO₄) and the volatiles were removed by evaporation. The solid was dissolved in methylene chloride/methanol and 5M hydrogen chloride in ether was added. The volatiles were removed under vacuum and the solid was dried under vacuum to give 6-methoxy-7-((1-

- 74 -

methyl(piperidin-4-yl)methoxy)-4-(5-phenylpyrazol-3-ylamino)quinazoline hydrochloride (160mg, 72%).

MS - ESI: 445 [MH]⁺

¹H NMR Spectrum: (DMSO_d₆) 1.6-1.8(m, 2H), 2.0-2.1(d, 2H), 2.1-2.2(m, 1H), 2.75(s, 3H),

5 3.0(m, 2H), 3.45(m, 2H), 4.0(s, 3H), 4.1(d, 2H), 7.21(s, 1H), 7.4(m, 1H), 7.45-7.55(m, 3H),
7.8(d, 2H), 8.3(s, 1H), 8.9(s, 1H)

Elemental analysis: Found C 52.2 H 6.3 N 14.4

C₂₅H₂₈N₆O₂ 2.2H₂O 2.4HCl Requires C 52.5 H 6.1 N 14.7%

10 Example 22

Using a procedure analogous to that described in Example 15, 4-chloro-6,7-dimethoxyquinazoline (224mg, 1mol), (prepared as described for the starting material in Example 1), was reacted with 3-amino-5-phenyl-4*H*-pyrazole (183mg, 1.16mol) to give 6,7-dimethoxy-4-(5-phenylpyrazol-3-ylamino)quinazoline hydrochloride (328mg, 94%).

15 MS - ESI: 348 [MH]⁺

¹H NMR Spectrum: (DMSO_d₆, CF₃COOD) 4.0(s, 6H), 7.28(s, 1H), 7.35(s, 1H), 7.41(t, 1H),
7.53(t, 2H), 7.81(d, 2H), 8.31(s, 1H), 8.99(s, 1H)

Elemental analysis: Found C 54.0 H 4.7 N 16.5

C₁₉H₁₇N₅O₂ 0.5H₂O 1.8HCl Requires C 54.1 H 4.7 N 16.6%

20

Example 23

A suspension of 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (150mg, 0.44mol), (prepared as described for the starting material in Example 2), and 3-(3-furyl)-4,5-dihydro-1*H*-pyrazol-5-one (80mg, 0.53mol) in DMF (2ml) containing potassium carbonate (92mg, 0.67mol) was heated at 100°C for 2.5 hours. After cooling, the mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried (MgSO₄) and evaporated. The residue was purified by chromatography eluting with ethyl acetate/methylene chloride (1/1) followed by methanol/ethyl acetate/methylene chloride (1/4/5), followed by methanol/methylene chloride (1/9) to give 4-(5-(3-furyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline hydrochloride (155mg, 77%).

- 75 -

¹H NMR Spectrum: (DMSO_d₆, CF₃COOD) 2.25-2.35(m, 2H), 3.2(t, 2H), 3.35(t, 2H), 3.55(d, 2H), 3.65(t, 2H), 4.05(d, 2H), 4.1(s, 3H), 4.4(t, 2H), 6.5(s, 1H), 6.95(s, 1H), 7.55(s, 1H), 7.7(s, 1H), 7.8(s, 1H), 8.15(s, 1H)

MS - ESI: 4.52 [MH]⁺

5

The starting material was prepared as follows:

Using an analogous procedure to that described for the preparation of the starting material in Example 9, ethyl 3-furoyl acetate (845mg, 4.64mmol) was reacted with hydrazine (0.25ml, 5.16mmol) to give 3-(3-furyl)-4,5-dihydro-1*H*-pyrazol-5-one (230mg, 30%).

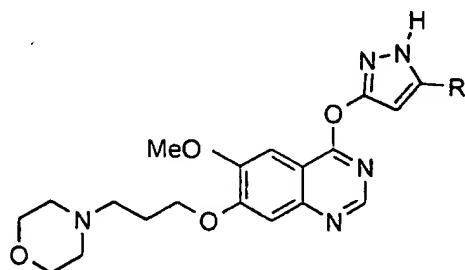
10 MS - ESI: 151 [MH]⁺

¹H NMR Spectrum: (DMSO_d₆, CF₃COOD) 6.15(s, 0.5H partly exchanged), 6.96(s, 1H), 7.84(s, 1H), 8.35(s, 1H)

Examples 24-31

15 Using an analogous procedure to that described in Example 23, 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline, (prepared as described for the starting material in Example 2), was reacted with the appropriate pyrazolone to give the compounds described in Table II hereinafter.

20 Table II



Example No.	weight obtained mg	yield %	R	[MH] ⁺	Note
24	100	47	2-fluorophenyl	480	1

25	65	29	3-nitrophenyl	507	2
26	65	29	4-nitrophenyl	507	3
27	60	32	propyl	428	4
28	60	44	pent-3-en-1-yl	454	5
29	42	33	methoxymethyl	430	6
30	33	26	ethyl	414	7
31	38	17	2-phenylethyl	490	8

Notes

- 1) 4-Chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline was reacted with 3-(2-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-5-one (95mg) to give Example 24.
- 5 ¹H NMR Spectrum: (DMSO_d₆, CF₃COOD) 2.25-2.4(m, 2H), 3.15(t, 2H), 3.35(t, 2H), 3.55(d, 2H), 3.7(t, 2H), 4.05(d, 2H), 4.1(s, 3H), 4.4(t, 2H), 6.65(s, 1H), 7.3-7.4(m, 3H), 7.4-7.5(m, 1H), 7.55(s, 1H), 7.7(s, 1H), 7.9(t, 1H), 8.98(s, 1H)

The starting material was prepared as follows:

- 10 Using an analogous procedure to that described for the preparation of the starting material in Example 9, ethyl 2-fluorobenzoyl acetate was reacted with hydrazine to give 3-(2-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-5-one (975mg, 48%).
- MS - ESI: 179 [MH]⁺
- 15 ¹H NMR Spectrum: (DMSO_d₆, CF₃COOD) 6.1(s, 0.5H, partly exchanged), 7.3-7.45(m, 2H), 7.45-7.55(m, 1H), 7.8-7.9(t, 1H)

2) 4-Chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline was reacted with 3-(3-nitrophenyl)-4,5-dihydro-1*H*-pyrazol-5-one (109mg) to give Example 25.

- 19 ¹H NMR Spectrum: (DMSO_d₆, CF₃COOD) 2.25-2.4(m, 2H), 3.1-3.25(t, 2H), 3.4(t, 2H), 3.55(d, 2H), 3.7(t, 2H), 4.05(d, 2H), 4.1(s, 3H), 4.4(t, 2H), 7.0(s, 1H), 7.55(s, 1H), 7.7(s, 1H), 7.8(t, 2H), 8.25(d, 2H), 8.7(s, 1H), 8.9(s, 1H)

The starting material was prepared as follows:

Using an analogous procedure to that described for the preparation of the starting material in Example 9, ethyl 3-nitrobenzoyl acetate was reacted with hydrazine to give 3-(3-nitrophenyl)-4,5-dihydro-1*H*-pyrazol-5-one (765mg, 72%).

MS - ESI: 205 [M.]⁺

- 5 ¹H NMR Spectrum: (DMSO_d₆, CF₃COOD) 6.32(s, 0.5H partly exchanged), 7.8(t, 1H), 8.2-8.3(m, 2H), 8.64(s, 1H)

3) 4-Chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline was reacted with 3-(4-nitrophenyl)-4,5-dihydro-1*H*-pyrazol-5-one (109mg) to give Example 26.

- 10 ¹H NMR Spectrum: (DMSO_d₆, CF₃COOD) 2.2-2.4(m, 2H), 3.1-3.2(m, 2H), 3.3-3.4(m, 2H), 3.55(d, 2H), 3.7(t, 2H), 4.02(d, 2H), 4.05(s, 3H), 4.35(t, 2H), 7.0(s, 1H), 7.5(s, 1H), 7.68(s, 1H), 8.1(d, 2H), 8.35(d, 2H), 8.82(s, 1H)

The starting material was prepared as follows:

- 15 Using an analogous procedure to that described for the preparation of the starting material in Example 9, ethyl 4-nitrobenzoyl acetate was reacted with hydrazine to give 3-(4-nitrophenyl)-4,5-dihydro-1*H*-pyrazol-5-one (630mg, 60%).

MS - ESI: 205 [M.]⁺

- 19 ¹H NMR Spectrum: (DMSO_d₆, CF₃COOD) 6.21(s, 0.5H partly exchanged), 8.03(d, 2H), 8.31(d, 2H)

4) 4-Chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline was reacted with 3-propyl-4,5-dihydro-1*H*-pyrazol-5-one (67mg) to give Example 27.

- 20 ¹H NMR Spectrum: (DMSO_d₆, CF₃COOD) 0.95(t, 3H), 1.65(q, 2H), 2.25-2.35(m, 2H), 2.62(t, 2H), 3.15(t, 2H), 3.3-3.4(m, 2H), 3.58(d, 2H), 3.7(t, 2H), 4.05(d, 2H), 4.05(s, 3H), 4.4(t, 2H), 6.05(s, 1H), 7.55(s, 1H), 7.7(s, 1H), 9.0(s, 1H)

The starting material was prepared as follows:

- 25 Using an analogous procedure to that described for the preparation of the starting material in Example 9, ethyl propylcarbonyl acetate was reacted with hydrazine to give 3-propyl-4,5-dihydro-1*H*-pyrazol-5-one (345mg, 53%).

MS - ESI: 127 [MH]⁺

¹H NMR Spectrum: (DMSOd₆, CF₃COOD) 0.95(t, 3H), 1.65(q, 2H), 2.6(t, 2H), 5.8(s, 0.5 H partly exchanged)

5) 4-Chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline was reacted with 3-pent-3-en-1-yl)-4,5-dihydro-1*H*-pyrazol-5-one (46mg) to give Example 28.

¹H NMR Spectrum: (DMSOd₆, CF₃COOD) 1.6 and 1.65(2d, 3H), 2.2-2.4(m, 4H), 2.7(t, 2H), 3.15(t, 2H), 3.4(t, 2H), 3.6(d, 2H), 3.7(t, 2H), 4.02(s, 3H), 4.05(d, 2H), 4.4(t, 2H), 5.4-5.5(m, 2H), 6.05(m, 1H), 7.5(s, 1H), 7.65(s, 1H), 8.9(br s, 1H).

10 6) 4-Chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline was reacted with 3-(methoxymethyl)-4,5-dihydro-1*H*-pyrazol-5-one (38mg), (DE2644588), to give Example 29.

¹H NMR Spectrum: (DMSOd₆, CF₃COOD) 2.3-2.4(m, 2H), 3.15(t, 2H), 3.3(s, 3H), 3.35(t, 2H), 3.55(d, 2H), 3.65(t, 2H), 4.02(s, 3H), 4.05(d, 2H), 4.4(t, 2H), 4.45(s, 2H), 6.20(s, 1H), 7.5(s, 1H), 7.55(s, 1H), 8.70(br s, 1H)

15

7) 4-Chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline was reacted with 3-ethyl-4,5-dihydro-1*H*-pyrazol-5-one (34mg), (Org. Synth. 1976, 55, 73), to give Example 30.

¹H NMR Spectrum: (DMSOd₆, CF₃COOD): 1.25(t, 3H), 2.3(m, 2H), 2.68(q, 2H), 3.15(t, 2H), 3.35(t, 2H), 3.55(d, 2H), 3.7(t, 2H), 4.05(s, 3H), 4.07(d, 2H), 4.35(t, 2H), 6.05(s, 1H), 7.5(s, 1H), 7.65(s, 1H), 8.8(s, 1H)

20

8) 4-Chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline was reacted with 3-(2-phenylethyl)-4,5-dihydro-1*H*-pyrazol-5-one (100mg) to give Example 31.

¹H NMR Spectrum: (DMSOd₆, CF₃COOD): 2.3(m, 2H), 3.0(s, 4H), 3.2(t, 2H), 3.35(t, 2H), 3.6(d, 2H), 3.7(t, 2H), 4.05(s, 3H), 4.1(d, 2H), 4.4(t, 2H), 6.05(s, 1H), 7.15-7.35(m, 6H), 7.5(s, 1H), 7.65(s, 1H), 8.9(s, 1H)

25

The starting material was prepared as follows:

Using an analogous procedure to that described for the preparation of the starting material in Example 9, 2-phenylethyl propylcarbonyl acetate (1g, 4.8mmol) was reacted with hydrazine to give 3-(2-phenylethyl)-4,5-dihydro-1*H*-pyrazol-5-one (741mg, 82%).

MS - ESI: 189 [MH]⁺

¹H NMR Spectrum: (DMSO_d₆) 2.75(m, 2H), 2.9(m, 2H), 5.25(s, 1H), 7.1-7.25(m, 3H), 7.25-7.35(m, 2H)

Example 32

5 Using a procedure analogous to that described in Example 15, 4-chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (140mg, 0.435mol), (prepared as described for the starting material in Example 15), was reacted with 3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-5-one (100mg, 0.52mol), (prepared as described for the starting material in Example 10), to give **6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-4-(5-(4-**

10 **methoxyphenyl)pyrazol-3-yl)quinazoline** (174mg, 84%).

MS - ESI: 476 [M+]⁺

¹H NMR Spectrum: (DMSO_d₆, CF₃COOD) 1.55-1.75(m, 2H), 2.05(d, 2H), 2.1-2.3(m, 1H), 2.82(s, 3H), 3.05(t, 2H), 3.55(d, 2H), 3.8(s, 3H), 4.1(s, 3H), 4.25(d, 2H), 6.6(s, 1H), 7.07(d, 2H), 7.58(s, 1H), 7.75(s, 1H), 7.75(d, 2H), 9.1(br s, 1H)

15 Elemental analysis: Found C 64.6 H 6.1 N 14.7
 $C_{26}H_{29}N_5O_4 \cdot 0.4H_2O$ Requires C 64.7 H 6.2 N 14.5%

Example 33

Using a procedure analogous to that described in Example 23, 4-chloro-6-methoxy-7-(2-(1,2,3-triazol-1-yl)ethoxy)quinazoline (160mg, 0.52mol) was reacted with 3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-5-one (120mg, 0.63mol), (prepared as described for the starting material in Example 10), to give **4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)-6-methoxy-7-(2-(1,2,3-triazol-1-yl)ethoxy)quinazoline** (105mg, 44%).

MS - ESI: 460 [M+]⁺

25 ¹H NMR Spectrum: (DMSO_d₆, CF₃COOD) 3.84(s, 3H), 4.07(s, 3H), 4.78(t, 2H), 5.02(t, 2H), 6.6(s, 1H), 7.07(d, 2H), 7.6(s, 1H), 7.74(d, 1H), 7.78(s, 1H), 7.82(s, 1H), 8.26(s, 1H), 9.17(s, 1H)

Elemental analysis: Found C 58.5 H 4.6 N 20.8
 $C_{25}H_{21}N_7O_4 \cdot 0.6H_2O$ Requires C 58.7 H 4.8 N 20.9%

30

The starting material was prepared as follows:

Triphenylphosphine (2.82g, 10.7mmol) was added to a solution of 2-(1,2,3-triazol-1-yl)ethanol (609mg, 5.4mmol), (J. Antib. 1993, 46, 177), and 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (1.1g, 3.6mmol), (prepared as described for the starting material in Example 7), in methylene chloride (70ml). diethyl

5 azodicarboxylate (600 μ l, 10.7mmol) was then added. After stirring for 2 hours at ambient temperature, the volatiles were removed by evaporation and the residue was purified by column chromatography eluting with methylene chloride/methanol (98/2) to give 6-methoxy-3-((pivaloyloxy)methyl)-7-(2-(1,2,3-triazol-1-yl)ethoxy)-3,4-dihydroquinazolin-4-one (4g, 97%).

10 5.1M Ammonia in methanol (30ml) was added to a solution of 6-methoxy-3-((pivaloyloxy)methyl)-7-(2-(1,2,3-triazol-1-yl)ethoxy)-3,4-dihydroquinazolin-4-one (1.4g, 3.5mmol) in a solution of methanol (30ml). After stirring overnight at ambient temperature, the volatiles were removed by evaporation and the residue was triturated with ether, collected by filtration, washed with ether and dried under vacuum to give 6-methoxy-7-(2-(1,2,3-triazol-1-yl)ethoxy)quinazoline (946mg, 92%).

15 ^1H NMR Spectrum: (DMSO $_d_6$, CF $_3$ COOD) 3.9(s, 3H); 4.6(t, 2H); 4.9(t, 2H); 7.25(s, 1H); 7.52(s, 1H); 7.77(s, 1H); 8.19(s, 1H); 8.9(s, 1H)

MS - ESI: 170 [MH] $^+$

20 A solution of 6-methoxy-7-(2-(1,2,3-triazol-1-yl)ethoxy)quinazoline (920mg, 3.2mmol) in thionyl chloride (10ml) containing DMF (0.9ml) was heated at 80°C for 1 hour. After evaporation of the volatiles, the residue was azeotroped with toluene. The residue was partitioned between ethyl acetate and water and the aqueous layer was adjusted to pH8 with solid sodium hydrogen carbonate. The organic layer was washed with water, brine, dried (MgSO_4), and the volatiles were removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (96/4) to give 4-chloro-6-methoxy-7-(2-(1,2,3-triazol-1-yl)ethoxy)quinazoline (693mg, 71%).

25 ^1H NMR Spectrum: (CDCl $_3$) 4.1(s, 3H); 4.55(t, 2H); 4.95(t, 2H); 7.3(s, 1H); 7.4(s, 1H); 7.75(s, 1H); 7.95(s, 1H); 8.85(s, 1H)

MS - EI: 305 [MH] $^+$

30 Elemental analysis: Found C 51.0 H 4.0 N 22.6%
C₁₃H₁₂N₅O₂Cl Requires C 51.0 H 3.9 N 22.9%

Example 34

A suspension of 4-chloro-6-methoxy-7-(1-(2-methylsulphonylethyl)piperidin-4-ylmethoxy)quinazoline (115mg, 0.28mol) and 3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-5-one (65mg, 0.33mol), (prepared as described for the starting material in Example 10), in 5 DMF (1.5ml) containing potassium carbonate (60mg, 0.42mol) was heated at 100°C for 30 minutes. After cooling, water was added. The precipitate was collected by filtration, washed with water and dried under vacuum. The solid was dissolved in methylene chloride/methanol and pentane was added. The precipitate was collected by filtration, washed with pentane and dried under vacuum to give 4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)-6-methoxy-7-(1-(2-methylsulphonylethyl)piperidin-4-ylmethoxy)quinazoline (120mg, 75%).

MS - ESI: 568 [MH]⁺

¹H NMR Spectrum: (DMSO_d₆, CF₃COOD) 1.3-1.4(m, 2H), 1.8-1.9(m, 3H), 2.0(t, 2H), 2.7(t, 2H), 2.95(d, 2H), 3.05(s, 3H), 3.25-3.3(m, 2H), 3.8(s, 3H), 4.0(s, 3H), 4.1(d, 2H), 6.6(s, 1H), 7.05(d, 2H), 7.4(s, 1H), 7.55(s, 1H), 7.7(d, 2H), 8.6(s, 1H)

15 Elemental analysis: Found C 57.1 H 5.9 N 12.1
C₂₈H₃₃N₅O₆S 0.6H₂O Requires C 58.1 H 6.0 N 12.1%

The starting material was prepared as follows:

A suspension of 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (6.12g, 20mmol), (prepared as described for the starting material in Example 7) and potassium carbonate (5.52g, 40mmol) in DMF (60ml) was stirred at ambient temperature for 30 minutes. 4-(4-Methylphenylsulphonyloxymethyl)-1-tert-butyloxycarbonylpiperidine (8.86g, 24mmol), (prepared as described for the starting material in Example 15), was added and the mixture was stirred at 100°C for 2 hours. After cooling, 25 the mixture was poured onto water/ice (400ml, 1/1) containing 2M hydrochloric acid (10ml). The precipitate was collected by filtration, washed with water and dried under vacuum over phosphorus pentoxide. The solid was triturated in a mixture of ether/pentane (1/1), collected by filtration and dried to give 6-methoxy-3-((pivaloyloxy)methyl)-7-((1-tert-butyloxycarbonylpiperidin-4-yl)methoxy)-3,4-dihydroquinazolin-4-one (7.9g, 78.5%).
30 ¹H NMR Spectrum: (DMSO_d₆) 1.1(s, 9H); 1.1-1.3(m, 2H); 1.42(s, 9H); 1.73(d, 2H); 1.93-2.1(br s, 1H); 2.65-2.9(br s, 2H); 3.9(s, 3H); 3.9-4.1(m, 4H); 5.9(s, 2H); 7.2(s, 1H); 7.5(s, 1H); 8.35(s, 1H)

MS (ESI): 526 [MNa]⁺

A solution of 6-methoxy-3-((pivaloyloxy)methyl)-7-((1-tert-butylloxycarbonylpiperidin-4-yl)methoxy)-3,4-dihydroquinazolin-4-one (7.9g, 16mmol) in methylene chloride (80ml) containing 5.5M hydrogen chloride in isopropanol (80ml) was stirred for 1 hour at ambient temperature. Ether was added and the solid was collected by filtration, washed with ether and dried under vacuum at 60°C to give 6-methoxy-7-((piperidin-4-yl)methoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one hydrochloride (6.9g, 100%).

¹H NMR Spectrum: (DMSO_d₆, CF₃CO₂D) 1.15(s, 9H); 1.5-1.7(m, 2H); 2.0(d, 2H); 2.2-2.3(br s, 1H); 3.0(t, 2H); 3.4(d, 2H); 3.94(s, 3H); 4.15(d, 2H); 5.97(s, 2H); 7.3(s, 1H); 7.6(s, 1H); 8.65(s, 1H)

MS (ESI): 404 [MH]⁺

Potassium carbonate (280mg, 2mmol) and methyl vinyl sulfone (0.4ml, 2.1mmol) were added to a solution of 6-methoxy-7-((piperidin-4-yl)methoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one hydrochloride (0.88g, 2mmol) and triethylamine (0.3ml, 2.1mmol) in methanol (10ml) and methylene chloride (10ml). After stirring for 2 hours at ambient temperature, the volatiles were removed under vacuum. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried (MgSO₄) and evaporated to give 6-methoxy-7-((1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (0.55g, 54%).

¹H NMR Spectrum: (DMSO_d₆) 1.09(s, 9H); 1.25-1.4(m, 2H); 1.7-1.9(m, 3H); 2.0(t, 2H); 2.7(t, 2H); 2.95(d, 2H); 3.02(s, 3H); 3.25-3.45(m, 2H); 3.9(s, 3H); 4.0(d, 2H); 5.9(s, 2H); 7.15(s, 1H); 7.49(s, 1H); 8.35(s, 1H)

MS (ESI): 510 [MH]⁺.

2M Aqueous sodium hydroxide (180μl, 0.35mmol) was added to a suspension of 6-methoxy-7-((1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (90mg, 0.18mmol) in methanol (3ml). After stirring for 2 hours at ambient temperature, the mixture was adjusted to pH10 with 2M hydrochloric acid. The volatiles were removed under vacuum and the residue was suspended in water, filtered, washed with water followed by ether and dried under vacuum at 60°C to give 6-methoxy-7-((1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy)-3,4-dihydroquinazolin-4-one (55mg, 79%).

¹H NMR Spectrum: (DMSO_d₆) 1.2-1.4(m, 2H); 1.7-1.85(m, 3H); 2.0(t, 2H); 2.7(t, 2H); 2.9(d, 2H); 3.02(s, 3H); 3.3-3.5(m, 2H); 3.9(s, 3H); 4.0(d, 2H); 7.11(s, 1H); 7.45(s, 1H); 7.97(s, 1H)
MS (ESI): 396 [MH]⁺

A solution of 6-methoxy-7-((1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy)-3,4-dihydroquinazolin-4-one (335mg, 0.85mmol) in thionyl chloride (5ml) containing DMF (50μl) was heated at reflux for 1 hour. After cooling, the volatiles were removed under vacuum and the residue was triturated with ether and filtered. The solid was suspended in methylene chloride and sodium hydrogen carbonate was added. The organic layer was washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was triturated with ether, filtered and dried under vacuum to give 4-chloro-6-methoxy-7-((1-(2-methylsulphonylethyl)piperidin-4-ylmethoxy)quinazoline (335mg, 95%).

¹H NMR Spectrum: (DMSO_d₆) 1.25-1.45(m, 2H); 1.75-1.90(m, 3H); 2.0(t, 2H); 2.7(t, 2H); 2.92(d, 2H); 3.03(s, 3H); 3.2-3.35(m, 2H); 4.0(s, 3H); 4.1(d, 2H); 7.40(s, 1H); 7.45(s, 1H); 8.9(s, 1H)
MS (ESI): 414 [MH]⁺

Example 35

Using a procedure analogous to that described in Example 14, 4-chloro-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline (350mg, 1mol), (prepared as described for the starting material in Example 14), was reacted with 3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-5-one (380mg, 2mol), (prepared as described for the starting material in Example 10), to give 4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline (215mg, 43%).

MS - ESI: 505 [MH]⁺
¹H NMR Spectrum: (DMSO_d₆, CD₃COOD), (60°C), 2.3-2.4(m, 2H), 2.95(s, 3H), 3.45(t, 2H), 3.55-3.7(m, 8H), 3.8(s, 3H), 4.05(s, 3H), 4.4(t, 2H), 6.55(s, 1H), 7.05(d, 2H), 7.55(s, 1H), 7.75(d, 2H), 7.75(s, 1H), 8.9(s, 1H)

Example 36

A suspension of 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (150mg, 0.44mol), (prepared as described for the starting material in Example 2), and 3-isobutyl-4,5-dihydro-1*H*-pyrazol-5-one (75mg, 0.53mol), (Org. Synth. 1976, 55, 73), in DMF (2ml)

containing potassium carbonate (92mg, 0.67mol) was heated at 100°C for 2.5 hours. After cooling, water was added and the aqueous layer was adjusted to pH6.5 with 2M hydrochloric acid. Ethyl acetate was added. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and the volatiles were removed by evaporation. The residue was purified by column chromatography eluting with ethyl acetate/methylene chloride (1/1) followed by methanol/ethyl acetate/methylene chloride (1/4/5) and by methanol/methylene chloride (1/9) to give 4-(5-isobutylpyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (85mg, 43%).

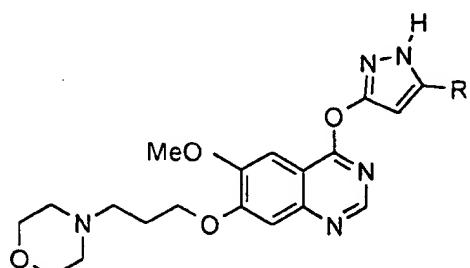
MS - ESI: 441 [MH]⁺

10 ¹H NMR Spectrum: (DMSO_d₆, CF₃COOD) 0.91(d, 6H), 1.9(m, 1H), 2.2-2.4(m, 2H), 3.15(t, 2H), 3.35(t, 2H), 3.55(d, 2H), 3.7(t, 2H), 4.03(d, 2H), 4.05(s, 3H), 4.35(t, 2H), 6.02(s, 1H), 7.55(s, 1H), 7.7(s, 1H), 9.1(s, 1H)

Examples 37-38

15 Using an analogous procedure to that described in Example 36, 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (150mg, 0.44mol), (prepared as described for the starting material in Example 2), was reacted with the appropriate pyrazolone to give the compounds described in Table III hereinafter.

Table III



20

Example No.	weight obtained mg	yield %	R	[MH] ⁺	Note
37	100	51	butyl	442	1
38	60	28	2-cyclopentylethyl	482	2

1) 4-Chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline was reacted with 3-butyl-4,5-dihydro-1*H*-pyrazol-5-one (75mg), (Synthesis, 1982, 12,1100), to give Example 37.

¹H NMR Spectrum: (DMSO_d₆, CF₃COOD): 0.9(t, 3H), 1.3-1.45(m, 2H), 1.55-1.7(m, 2H), 2.3-2.4(m, 2H), 2.6(t, 2H), 3.2(t, 2H), 3.35(t, 2H), 3.55(d, 2H), 3.7(t, 2H), 4.02(s, 3H), 4.04(d,

5 2H), 4.35(t, 2H), 6.0(s, 1H), 7.5(s, 1H), 7.66(s, 1H), 8.95(s, 1H)

2) 4-Chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline was reacted with 3-(2-cyclopentylethyl)-4,5-dihydro-1*H*-pyrazol-5-one (96 mg) to give Example 38.

¹H NMR Spectrum: (DMSO_d₆, CF₃COOD): 1.05-1.2(m, 2H), 1.4-1.9(m, 11H), 2.3(br s, 2H),
10 2.65(t, 2H), 3.15(br s, 2H), 3.35(t, 2H), 3.55(d, 2H), 3.7(t, 2H), 4.0(s, 3H), 4.02(d, 2H),
4.35(br s, 2H), 6.0(s, 1H), 7.5(s, 1H), 7.65(s, 1H), 8.9(s, 1H)

The starting material was prepared as follows:

3-Cyclopentylpropionyl chloride (0.64ml, 4.16mmol) was added to a solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (500mg, 3.47mmol) in anhydrous methylene chloride (10ml). After cooling to 0°C, pyridine (0.56ml, 6.94mmol) was added in portions. After stirring for 1 hour at 0°C and 2 hours at ambient temperature the mixture was poured onto water (20ml) containing concentrated hydrochloric acid (0.5ml). The organic layer was separated, washed with water, brine, dried (MgSO₄) and the volatiles were removed by evaporation to give 5-(3-cyclopentylpropionyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (900mg, 96%).

¹H NMR Spectrum: (CDCl₃) 1.0-1.2(m, 4H), 1.45-1.9(m, 11H), 2.35-2.55(m, 2H), 3.1(t, 2H)

A solution of 5-(3-cyclopentylpropionyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (900mg, 3.3mmol) in ethanol (5ml) containing hydrazine (0.43ml, 8.84mmol) was stirred at ambient temperature for 20 minutes followed by stirring for 2 hours at 75°C. The volatiles were removed under vacuum and the residue was triturated with ether. The solid was collected by filtration, washed with ether and dried under vacuum to give 3-(2-cyclopentylethyl)-4,5-dihydro-1*H*-pyrazol-5-one (250mg, 42%).

MS - ESI: 181 [MH]⁺

¹H NMR Spectrum: (DMSO_d₆, CF₃COOD) 1.0-1.2(m, 2H), 1.4-1.8(m, 9H), 2.6(t, 2H), 5.8(s,
30 0.5H partly exchanged)

Example 39

Using a procedure analogous to that described in Example 34. 4-chloro-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline (150mg. 0.45mol) was reacted with 3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-5-one (105mg, 0.54mol), (prepared as described for the starting material in Example 10), to give 4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline (220mg, 91%).

MS - ESI: 485 [MH]⁺

¹H NMR Spectrum: (DMSO_d₆, CF₃COOD): 2.35(m, 2H), 3.05(s, 3H), 3.35(t, 2H), 3.8(s, 3H), 4.1(s, 3H), 4.4(t, 2H), 6.6(s, 1H), 7.05(d, 2H), 7.55(s, 1H), 7.7(d, 2H), 7.74(s, 1H), 9.14(s, 1H)

Elemental analysis:

10	C ₂₃ H ₂₄ N ₄ O ₆ S, 0.1H ₂ O	Found	C 56.5	H 5.3	N 11.6
		Requires	C 56.8	H 5.0	N 11.5%

The starting material was prepared as follows:

Triphenylphosphine (8.9g, 35.2mmol) was added to a suspension of 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (6g, 19.6mmol), (prepared as described for the starting material in Example 7), in methylene chloride (150ml). This was followed by the addition of 3-methylsulphonylpropanol (3.5g, 25.4mmol) and diethylazodicarboxylate (5.55ml, 35.2mmol) in portions. The reaction was complete once the reaction became homogeneous. Silica was added and the volatiles were removed by evaporation. The free flowing powder was placed on the top of a flash chromatography column pre-equilibrated with ethyl acetate (100%). Elution was done using ethyl acetate (100%) followed by methylene chloride/ethyl acetate/methanol (60/35/5). The volatiles were removed by evaporation to give 6-methoxy-7-(3-methylsulphonylpropoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (7.58 g, 91%) as a white solid.

¹H NMR Spectrum: (CDCl₃) 1.2(s, 9H); 2.4-2.5(m, 2H); 3.0(s, 3H); 3.25-3.35(t, 2H); 5.95(s, 1H); 7.1(s, 1H); 7.65(s, 1H); 8.2(s, 1H)

6-Methoxy-7-(3-methylsulphonylpropoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (7g, 17mmol) was suspended in methanol and 2M sodium hydroxide (3.3ml, 6.6mmol) was added with continuous stirring. The reaction mixture became homogeneous after 15 minutes. After a further 45 minutes water was added (7ml) and the reaction mixture was adjusted to pH10 with 2M hydrochloric acid. The precipitate (a white solid) was collected by filtration, washed with water and dried over phosphorus pentoxide

under vacuum to give 6-methoxy-7-(3-methylsulphonylpropoxy)-3,4-dihydroquinazolin-4-one (5 g, 90%).

¹H NMR Spectrum: (DMSO_d₆) 2.2-2.3(m, 2H); 3.05(s, 3H); 3.35(t, 2H); 3.9(s, 3H); 4.25(t, 2H); 7.15(s, 1H); 7.5(s, 1H); 8.0(s, 1H)

5 6-Methoxy-7-(3-methylsulphonylpropoxy)-3,4-dihydroquinazolin-4-one (3.6g, 11.5mmol) was suspended in thionyl chloride (40ml). DMF (1.8ml) was added under argon and the mixture was heated at reflux for 1.5 hours. The thionyl chloride was eliminated by several azeotropic distillations using toluene. The solid residue was suspended in ice/water and a saturated solution of sodium hydrogen carbonate was added to adjust the mixture to 10 pH7. The solid was collected by filtration, washed with water and dried in a vacuum dessicator over phosphorus pentoxide to give 4-chloro-6-methoxy-7-(3-methylsulphonylpropoxy) quinazoline (3.35g, 88%).

¹H NMR Spectrum: (DMSO_d₆) 2.2-2.3(m, 2H); 3.05(s, 3H); 3.3-3.4(m, 2H); 4.01(s, 3H); 4.4(t, 2H); 7.41(s, 1H); 7.47(s, 1H); 8.88(s, 1H)

15

Example 40

The following illustrate representative pharmaceutical dosage forms containing the compound of formula I, or a pharmaceutically acceptable salt thereof (hereafter compound X), for therapeutic or prophylactic use in humans:

20

(a)	<u>Tablet I</u>	<u>mg/tablet</u>
	Compound X	100
	Lactose Ph.Eur	182.75
	Croscarmellose sodium	12.0
25	Maize starch paste (5% w/v paste)	2.25
	Magnesium stearate	3.0

(b)	<u>Tablet II</u>	<u>mg/tablet</u>
	Compound X	50
30	Lactose Ph.Eur	223.75
	Croscarmellose sodium	6.0
	Maize starch	15.0

	Polyvinylpyrrolidone (5% w/v paste)	2.25
	Magnesium stearate	3.0
(c)	<u>Tablet III</u>	<u>mg/tablet</u>
5	Compound X	1.0
	Lactose Ph.Eur	93.25
	Croscarmellose sodium	4.0
	Maize starch paste (5% w/v paste)	0.75
	Magnesium stearate	1.0
10		
(d)	<u>Capsule</u>	<u>mg/capsule</u>
	Compound X	10
	Lactose Ph.Eur	488.5
	Magnesium stearate	1.5
15		
(e)	<u>Injection I</u>	<u>(50 mg/ml)</u>
	Compound X	5.0% w/v
	1N Sodium hydroxide solution	15.0% v/v
	0.1N Hydrochloric acid	
20	(to adjust pH to 7.6)	
	Polyethylene glycol 400	4.5% w/v
	Water for injection to 100%	
(f)	<u>Injection II</u>	<u>(10 mg/ml)</u>
25	Compound X	1.0% w/v
	Sodium phosphate BP	3.6% w/v
	0.1N Sodium hydroxide solution	15.0% v/v
	Water for injection to 100%	
30	(g) <u>Injection III</u>	<u>(1 mg/ml buffered to pH6)</u>
	Compound X	0.1% w/v
	Sodium phosphate BP	2.26% w/v

- 89 -

Citric acid	0.38% w/v
Polyethylene glycol 400	3.5% w/v
Water for injection to 100%	

5 Note

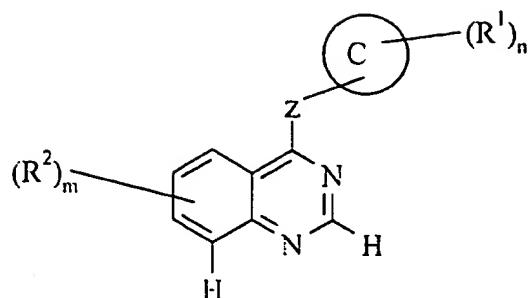
The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

CLAIMS:

1. The use of a compound of the formula I:

5

10



wherein:

15 ring C is a 5-6-membered heterocyclic moiety which may be saturated or unsaturated, which may be aromatic or non-aromatic, and which contains 1-3 heteroatoms selected independently from O, N and S;

Z is -O-, -NH-, -S- or -CH₂-;

15 R¹ represents hydrogen, C₁₋₄alkyl, C₁₋₄alkoxymethyl, di(C₁₋₄alkoxy)methyl, C₁₋₄alkanoyl, trifluoromethyl, cyano, amino, C₂₋₅alkenyl, C₂₋₅alkynyl, a phenyl group, a benzyl group or a 5-6-membered heterocyclic group with 1-3 heteroatoms, selected independently from O, S and N, which heterocyclic group may be aromatic or non-aromatic and may be saturated (linked via a ring carbon or nitrogen atom) or unsaturated (linked via a ring carbon atom), and which phenyl, benzyl or heterocyclic group may bear on one or more ring carbon atoms up to 5 substituents selected from hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkanoyloxy, trifluoromethyl, cyano, amino, nitro, C₂₋₄alkanoyl, C₁₋₄alkanoylamino, C₁₋₄alkoxycarbonyl, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphinyl, C₁₋₄alkylsulphonyl, carbamoyl, N-C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl, N,N-di(C₁₋₄alkyl)aminosulphonyl, C₁₋₄alkylsulphonylamino, C₁₋₄alkylamino, C₁₋₄hydroxyalkyl,

25 C₁₋₄aminoalkyl, C₁₋₄haloalkyl, C₁₋₄hydroxyalkoxy, carboxy and a saturated heterocyclic group selected from morpholino, thiomorpholino, pyrrolidinyl, piperazinyl, piperidinyl imidazolidinyl and pyrazolidinyl, which saturated heterocyclic group may bear 1 or 2

substituents selected from oxo, hydroxy, halogeno, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkanoyloxy, trifluoromethyl, cyano, amino, nitro and C₁₋₂alkoxycarbonyl; and additionally R¹ may represent carboxy, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₃alkyl, or phenylC₂₋₄alkyl wherein the phenyl moiety may bear up to 5 substituents selected from the list herein defined for a phenyl ring which is directly linked to ring C;

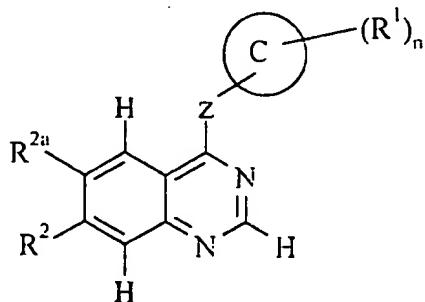
- 5 n is an integer from 0 to 5;
- m is an integer from 0 to 3;
- R² represents hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkylsulphonyl, -NR³R⁴ (wherein R³ and R⁴, which may be the same or different, each represents hydrogen or C₁₋₃alkyl), or R⁵X¹- (wherein X¹ represents a direct bond, -O-, -CH₂-, -OCO-, carbonyl, -S-, -SO₂-, -NR⁶CO-, -CONR⁷-, -SO₂NR⁸-, -NR⁹SO₂- or -NR¹⁰- (wherein R⁶, R⁷, R⁸, R⁹ and R¹⁰ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl), and R⁵ is selected from one of the following eighteen groups:
- 10 1) hydrogen or C₁₋₃alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, chloro, bromo and amino;
- 15 2) C₁₋₃alkylX²COR¹¹ (wherein X² represents -O- or -NR¹²- (in which R¹² represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹¹ represents C₁₋₃alkyl, -NR¹³R¹⁴ or -OR¹⁵ (wherein R¹³, R¹⁴ and R¹⁵ which may be the same or different each represents hydrogen, C₁₋₃alkyl, C₄₋₅alkyl or C₁₋₃alkoxyC₂₋₃alkyl));
- 20 3) C₁₋₃alkylX³R¹⁶ (wherein X³ represents -O-, -S-, -SO-, -SO₂-, -OCO-, -NR¹⁷CO-, -CONR¹⁸-, -SO₂NR¹⁹-, -NR²⁰SO₂- or -NR²¹- (wherein R¹⁷, R¹⁸, R¹⁹, R²⁰ and R²¹ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹⁶ represents hydrogen, C₁₋₃alkyl, cyclopentyl, cyclohexyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C₁₋₃alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C₁₋₄alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄cyanoalkyl and C₁₋₄alkoxycarbonyl);
- 25 4) C₁₋₃alkylX⁴C₁₋₃alkylX⁵R²² (wherein X⁴ and X⁵ which may be the same or different are each -O-, -S-, -SO-, -SO₂-, -NR²³CO-, -CONR²⁴-, -SO₂NR²⁵-, -NR²⁶SO₂- or -NR²⁷- (wherein R²³, R²⁴, R²⁵, R²⁶ and R²⁷ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²² represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl);

- 5) R^{28} (wherein R^{28} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-4} alkyl, C_{1-4} alkylsulphonyl C_{1-4} alkyl and C_{1-4} alkoxycarbonyl);
- 6) C_{1-5} alkyl R^{28} (wherein R^{28} is as defined herein);
- 7) C_{2-5} alkenyl R^{28} (wherein R^{28} is as defined herein);
- 8) C_{2-5} alkynyl R^{28} (wherein R^{28} is as defined herein);
- 9) R^{29} (wherein R^{29} represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents on an available carbon atom selected from hydroxy, halogeno, amino, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, C_{1-4} hydroxyalkoxy, carboxy, trifluoromethyl, cyano, -CONR³⁰R³¹ and -NR³²COR³³ (wherein R³⁰, R³¹, R³² and R³³, which may be the same or different, each represents hydrogen, C_{1-4} alkyl or C_{1-3} alkoxy C_{2-3} alkyl));
- 10) C_{1-5} alkyl R^{29} (wherein R^{29} is as defined herein);
- 11) C_{2-5} alkenyl R^{29} (wherein R^{29} is as defined herein);
- 12) C_{2-5} alkynyl R^{29} (wherein R^{29} is as defined herein);
- 13) C_{1-5} alkylIX⁶ R^{29} (wherein X⁶ represents -O-, -S-, -SO-, -SO₂-, -NR³⁴CO-, -CONR³⁵-, -SO₂NR³⁶-, -NR³⁷SO₂- or -NR³⁸- (wherein R³⁴, R³⁵, R³⁶, R³⁷ and R³⁸ each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R²⁹ is as defined herein);
- 14) C_{2-5} alkenylIX⁷ R^{29} (wherein X⁷ represents -O-, -S-, -SO-, -SO₂-, -NR³⁹CO-, -CONR⁴⁰-, -SO₂NR⁴¹-, -NR⁴²SO₂- or -NR⁴³- (wherein R³⁹, R⁴⁰, R⁴¹, R⁴² and R⁴³ each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R²⁹ is as defined herein);
- 15) C_{2-5} alkynylIX⁸ R^{29} (wherein X⁸ represents -O-, -S-, -SO-, -SO₂-, -NR⁴⁴CO-, -CONR⁴⁵-, -SO₂NR⁴⁶-, -NR⁴⁷SO₂- or -NR⁴⁸- (wherein R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁷ and R⁴⁸ each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R²⁹ is as defined herein);
- 16) C_{1-3} alkylIX⁹ C_{1-3} alkyl R^{29} (wherein X⁹ represents -O-, -S-, -SO-, -SO₂-, -NR⁴⁹CO-, -CONR⁵⁰-, -SO₂NR⁵¹-, -NR⁵²SO₂- or -NR⁵³- (wherein R⁴⁹, R⁵⁰, R⁵¹, R⁵² and R⁵³ each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R²⁹ is as defined herein);
- 17) C_{1-3} alkylIX⁹ C_{1-3} alkyl R^{28} (wherein X⁹ and R²⁸ are as defined herein); and

- 18) $C_{1,2}\text{alkyl}R^{54}C_{1,3}\text{alkyl}X^9R^{55}$ (wherein X^9 is as defined herein and R^{54} and R^{55} are each independently selected from hydrogen, $C_{1,3}\text{alkyl}$, cyclopentyl, cyclohexyl and a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which $C_{1,3}\text{alkyl}$ group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and $C_{1,4}\text{alkoxy}$ and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, $C_{1,4}\text{alkyl}$, $C_{1,4}\text{hydroxyalkyl}$, $C_{1,4}\text{alkoxy}$, $C_{1,4}\text{cyanoalkyl}$ and $C_{1,4}\text{alkoxycarbonyl}$), with the proviso that R^{54} cannot be hydrogen; and additionally wherein any $C_{1,5}\text{alkyl}$, $C_{2,5}\text{alkenyl}$ or $C_{2,5}\text{alkynyl}$ group in R^5X^1 - may bear one or more substituents selected from hydroxy, halogeno and amino;
- 5 or a salt thereof in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

2. The use of a compound of the formula Ia:

15



20

(Ia)

wherein:

ring C, R^1 , R^2 , n and Z are as defined in claim 1 with the proviso that R^2 is not hydrogen; and

25 R^{2a} represents hydrogen, halogeno, $C_{1,3}\text{alkyl}$, $C_{1,3}\text{alkoxy}$, $C_{1,3}\text{alkylthio}$, $-\text{NR}^{3a}\text{R}^{4a}$ (wherein R^{3a} and R^{4a} , which may be the same or different, each represents hydrogen or $C_{1,3}\text{alkyl}$), or $R^{5a}(\text{CH}_2)_{za}X^{1a}$ (wherein R^{5a} is a 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, $C_{1,4}\text{alkyl}$, $C_{1,4}\text{hydroxyalkyl}$ and $C_{1,4}\text{alkoxy}$, za is an integer from 0 to 4 and X^{1a} represents a direct bond, $-\text{O}-$, $-\text{CH}_2-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{NR}^{6a}\text{CO}-$, $-\text{CONR}^{7a}-$, $-\text{SO}_2\text{NR}^{8a}-$, $-\text{NR}^{9a}\text{SO}_2-$ or $-\text{NR}^{10a}-$ (wherein R^{6a} , R^{7a} , R^{8a} , R^{9a} and R^{10a} each independently represents hydrogen, $C_{1,3}\text{alkyl}$ or $C_{1,3}\text{alkoxyC}_{2,3}\text{alkyl}$));

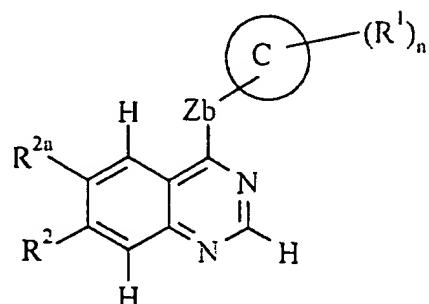
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or a salt thereof, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

5

3. The use of a compound of the formula Ib:

10



(Ib)

15

wherein:

ring C, R^1 , R^2 and n are as defined in claim 1 with the proviso that R^2 is not hydrogen, R^{2a} is as defined in claim 2; and

Zb is -O- or -S-;

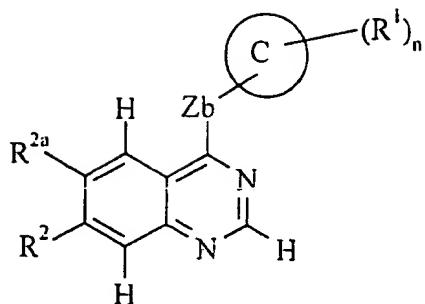
or a salt thereof, in the manufacture of a medicament for use in the production of an

20 antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

4. A compound of the formula II:

25

5



wherein:

- 10 ring C, R¹, R² and n are as defined in claim 1 with the proviso that R² does not have any of the following values:
 hydrogen, substituted or unsubstituted C₁₋₅alkyl, halogeno, C₁₋₅alkoxy, phenoxy or phenylC₁₋₅alkoxy;
- R^{2a} is as defined in claim 2; and
- 15 Zb is as defined in claim 3;
 or a salt thereof.

5. A compound as claimed in claim 4 wherein Zb is -O-.
- 20 6. A compound as claimed in claim 4 or claim 5 wherein R^{2a} is methoxy.
7. A compound as claimed in any one of claims 4-6 wherein ring C is a 5-membered heteroaromatic moiety which contains 1-3 heteroatoms selected independently from O, N and S.
- 25 8. A compound as claimed in any one of claims 4-7 wherein R¹ is a phenyl group or a 5-6-membered heteroaromatic group with 1-3 heteroatoms, selected independently from O, S and N, (linked via a ring carbon atom), which phenyl or heteroaromatic group is optionally substituted as defined in claim 1.
- 30

9. A compound as claimed in any one of claims 4-8 wherein R² represents hydroxy, halogeno, nitro, trifluoromethyl, C₁₋₃alkyl, cyano, amino or R⁵X¹- [wherein X¹ is as defined in claim 1 and R⁵ is selected from one of the following eighteen groups:

- 1) C₁₋₄alkyl which may be unsubstituted or substituted with one or more fluorine atoms, or C₂₋₅alkyl which may be unsubstituted or substituted with 1 or 2 groups selected from hydroxy and amino;
- 2) C₂₋₃alkylX²COR¹¹ (wherein X² is as defined in claim 1 and R¹¹ represents -NR¹³R¹⁴ or -OR¹⁵ (wherein R¹³, R¹⁴ and R¹⁵ which may be the same or different are each C₁₋₂alkyl or C₁₋₂alkoxyethyl));
- 3) C₂₋₄alkylX³R¹⁶ (wherein X³ is as defined in claim 1 and R¹⁶ is a group selected from C₁₋₃alkyl, cyclopentyl, cyclohexyl, pyrrolidinyl and piperidinyl which group is linked to X³ through a carbon atom and which C₁₋₃alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C₁₋₂alkoxy and which cyclopentyl, cyclohexyl, pyrrolidinyl or piperidinyl group may carry one substituent selected from oxo, hydroxy, halogeno, C₁₋₂alkyl, C₁₋₂hydroxyalkyl and C₁₋₂alkoxy);
- 4) C₂₋₃alkylX⁴C₂₋₃alkylX⁵R²² (wherein X⁴ and X⁵ are as defined in claim 1 and R²² represents hydrogen or C₁₋₃alkyl);
- 5) C₁₋₄alkylR⁵⁹ (wherein R⁵⁹ is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithiolan-2-yl and 1,3-dithian-2-yl, which group is linked to C₁₋₄alkyl through a carbon atom and which group may carry 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₃alkyl, C₁₋₃hydroxyalkyl, C₁₋₃alkoxy, C₁₋₂alkoxyC₁₋₃alkyl and C₁₋₂alkylsulphonylC₁₋₃alkyl) or C₂₋₄alkylR⁶⁰ (wherein R⁶⁰ is a group selected from morpholino, thiomorpholino, pyrrolidin-1-yl, piperazin-1-yl and piperidino which group may carry 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₃alkyl, C₁₋₃hydroxyalkyl, C₁₋₃alkoxy, C₁₋₂alkoxyC₁₋₃alkyl and C₁₋₂alkylsulphonylC₁₋₃alkyl);
- 6) C₃₋₄alkenylR⁶¹ (wherein R⁶¹ represents R⁵⁹ or R⁶⁰ as defined herein);
- 7) C₃₋₄alkynylR⁶¹ (wherein R⁶¹ represents R⁵⁹ or R⁶⁰ as defined herein);
- 8) R²⁹ (wherein R²⁹ is as defined in claim 1);
- 9) C₁₋₄alkylR²⁹ (wherein R²⁹ is as defined in claim 1);
- 10) 1-R²⁹prop-1-en-3-yl or 1-R²⁹but-2-en-4-yl (wherein R²⁹ is as defined in claim 1 with the proviso that when R⁵ is 1-R²⁹prop-1-en-3-yl, R²⁹ is linked to the alkenyl group via a carbon atom);

- 11) 1-R²⁹prop-1-yn-3-yl or 1-R²⁹but-2-yn-4-yl (wherein R²⁹ is as defined in claim 1 with the proviso that when R⁵ is 1-R²⁹prop-1-yn-3-yl, R²⁹ is linked to the alkynyl group via a carbon atom);
- 12) C_{1,5}alkylX⁶R²⁹ (wherein X⁶ and R²⁹ are as defined in claim 1);
- 5 13) 1-(R²⁹X⁷)but-2-en-4-yl (wherein X⁷ and R²⁹ are as defined in claim 1);
- 14) 1-(R²⁹X⁸)but-2-yn-4-yl (wherein X⁸ and R²⁹ are as defined in claim 1);
- 15) C_{2,5}alkylX⁹C_{1,2}alkylIR²⁹ (wherein X⁹ and R²⁹ are as defined in claim 1);
- 16) R²⁸ (wherein R²⁸ is as defined in claim 1);
- 17) C_{2,5}alkylX⁹C_{1,2}alkylIR²⁸ (wherein X⁹ and R²⁸ are as defined in claim 1); and
- 10 18) C_{2,5}alkylR⁵⁴C_{1,2}alkylX⁹R⁵⁵ (wherein X⁹, R⁵⁴ and R⁵⁵ are as defined in claim 1);
and additionally wherein any C_{1,5}alkyl, C_{2,5}alkenyl or C_{2,5}alkynyl group in R⁵X¹- may bear one or more substituents selected from hydroxy, halogeno and amino].

10. A compound as claimed in any one of claims 4-9 wherein R² represents 2-methoxyethoxy, 2-(2-methoxyethoxy)ethoxy, 3-methoxypropoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, 2-(tetrahydropyran-4-yloxy)ethoxy, 3-(tetrahydropyran-4-yloxy)propoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy, 2-(1,1-dioxothiomorpholino)ethoxy, 3-(1,1-dioxothiomorpholino)propoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, 2-(N-methoxyacetyl-N-methylamino)ethoxy, 3-(N-methoxyacetyl-N-methylamino)propoxy, N-methylpiperidin-3-ylmethoxy, 4-(pyrrolidin-1-yl)but-2-en-yloxy, 2-(2-oxopyrrolidin-1-yl)ethoxy, 3-(2-oxopyrrolidin-1-yl)propoxy, 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propoxy, 2-(2-(pyrrolidin-1-yl)ethoxy)ethoxy, 2-(2-(4-methylpiperazin-1-yl)ethoxy)ethoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-(methylpiperidino)ethoxy, 3-(methylpiperidino)propoxy, 2-(ethylpiperidino)ethoxy, 3-(ethylpiperidino)propoxy, 2-((2-methoxyethyl)piperidino)ethoxy, 3-((2-methoxyethyl)piperidino)propoxy, 2-((2-methylsulphonyl)ethylpiperidino)ethoxy, 3-((2-methylsulphonyl)ethylpiperidino)propoxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-(piperidin-3-yl)ethoxy, 2-(piperidin-4-yl)ethoxy, 3-(piperidin-3-yl)propoxy, 3-(piperidin-4-yl)propoxy, 2-(methylpiperidin-3-yl)ethoxy, 2-(methylpiperidin-4-yl)ethoxy, 3-(methylpiperidin-3-yl)propoxy, 3-(methylpiperidin-4-yl)propoxy, 2-(ethylpiperidin-3-yl)ethoxy, 2-(ethylpiperidin-4-yl)ethoxy, 3-(ethylpiperidin-3-yl)propoxy, 3-(ethylpiperidin-4-yl)propoxy,

- yl)propoxy, 2-((2-methoxyethyl)piperidin-3-yl)ethoxy, 2-((2-methoxyethyl)piperidin-4-yl)ethoxy, 3-((2-methoxyethyl)piperidin-3-yl)propoxy, 3-((2-methoxyethyl)piperidin-4-yl)propoxy, 2-((2-methylsulphonylethyl)piperidin-3-yl)ethoxy, 2-((2-methylsulphonylethyl)piperidin-4-yl)ethoxy, 3-((2-methylsulphonylethyl)piperidin-3-yl)propoxy, 3-((2-methylsulphonylethyl)piperidin-4-yl)propoxy, 1-isopropylpiperidin-2-ylmethyl, 1-isopropylpiperidin-3-ylmethyl, 1-isopropylpiperidin-4-ylmethyl, 2-(1-isopropylpiperidin-2-yl)ethyl, 2-(1-isopropylpiperidin-3-yl)ethyl, 2-(1-isopropylpiperidin-4-yl)ethyl, 3-(1-isopropylpiperidin-2-yl)propyl, 3-(1-isopropylpiperidin-3-yl)propyl, 3-(1-isopropylpiperidin-4-yl)propyl, 3-(4-methylpiperazin-1-yl)propoxy, 1-methylpiperidin-4-ylmethoxy, 1-(2-methylsulphonylethyl)piperidin-4-ylmethoxy, 1-(2-pyrrolidinylethyl)piperidin-4-ylmethoxy, 1-(3-pyrrolidinylpropyl)piperidin-4-ylmethoxy, 1-(2-piperidinylethyl)piperidin-4-ylmethoxy, 1-(3-piperidinylpropyl)piperidin-4-ylmethoxy, 1-(2-morpholinoethyl)piperidin-4-ylmethoxy, 1-(3-morpholinopropyl)piperidin-4-ylmethoxy, 1-(2-thiomorpholinoethyl)piperidin-4-ylmethoxy, 1-(3-thiomorpholinopropyl)piperidin-4-ylmethoxy, 1-(2-azetidinylethyl)piperidin-4-ylmethoxy or 1-(3-azetidinylpropyl)piperidin-4-ylmethoxy.

11. A compound as claimed in claim 4 selected from:

- 4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline,
20
4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline,
4-(5-(3-furyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline,
4-(5-(4-chlorophenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
25
6-methoxy-7-(3-morpholinopropoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline,
7-(2-(imidazol-1-yl)ethoxy)-6-methoxy-4-(5-phenylpyrazol-3-yloxy)quinazoline,
4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline,
6-methoxy-7-(2-methoxyethoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline,
30
4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)-6-methoxy-7-(2-(1,2,3-triazol-1-yl)ethoxy)quinazoline and

4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)-6-methoxy-7-(1-(2-methylsulphonylethyl)piperidin-4-ylmethoxy)quinazoline,
and salts thereof.

5 12. A compound as claimed in claim 4 selected from:

7-(2-methoxyethoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline,
4-(5-(2-fluorophenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
6-methoxy-7-(3-morpholinopropoxy)-4-(5-(3-nitrophenyl)pyrazol-3-yloxy)quinazoline,
6-methoxy-7-(3-morpholinopropoxy)-4-(5-(4-nitrophenyl)pyrazol-3-yloxy)quinazoline,
10 6-methoxy-7-(3-morpholinopropoxy)-4-(5-(4-pyridyl)pyrazol-3-yloxy)quinazoline,
4-(5-(4-fluorophenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline, and
6-methoxy-7-(2-methoxyethoxy)-4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)quinazoline,
and salts thereof.

15 13. The use of a compound as claimed in claim 1 selected from:

6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)-4-(5-phenylpyrazol-3-ylamino)quinazoline

and

6,7-dimethoxy-4-(5-phenylpyrazol-3-yloxy)quinazoline

or a salt thereof, in the manufacture of a medicament for use in the production of an

20 antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as
humans.

14. A compound as claimed in any one of claims 4 to 12 in the form of a
pharmaceutically acceptable salt.

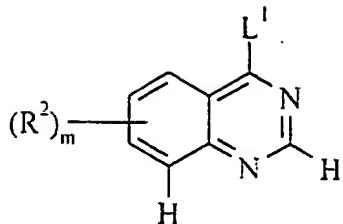
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15. A process for the preparation of a compound of formula I or salt thereof
which comprises:

(a) the reaction of a compound of the formula III:

- 100 -

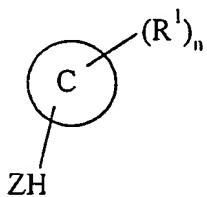
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(III)

(wherein R^2 and m are as defined in claim 1 and L^1 is a displaceable moiety), with a compound of the formula IV:

10

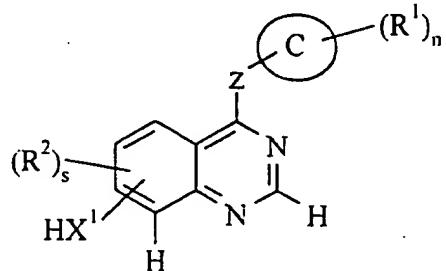


(IV)

(wherein ring C, R^1 , Z and n are as defined in claim 1);

- 15 (b) compounds of formula I and salts thereof wherein at least one R^2 is R^5X^1 wherein R^5 is as defined in claim 1 and X^1 is -O-, -S-, -OCO- or -NR¹⁰- (wherein R^{10} independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) may be prepared by the reaction of a compound of the formula V:

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(V)

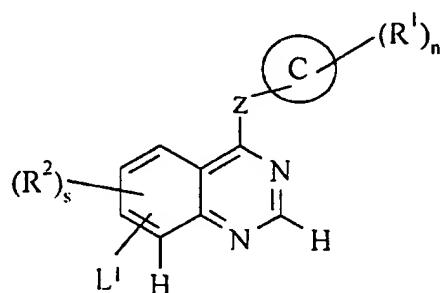
(wherein ring C, Z, R^1 , R^2 and n are as defined in claim 1 and X^1 is as defined herein in this section and s is an integer from 0 to 2) with a compound of formula VI:



(wherein R^s is as defined in claim 1 and L^1 is as defined herein);

- 5 (c) compounds of the formula I and salts thereof wherein at least one R^2 is R^sX^1 wherein R^s is as defined in claim 1 and X^1 is -O-, -S-, -OCO- or -NR¹⁰- (wherein R^{10} represents hydrogen, $C_{1,3}$ alkyl or $C_{1,3}$ alkoxyC_{2,3}alkyl) may be prepared by the reaction of a compound of the formula VII:

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with a compound of the formula VIII:

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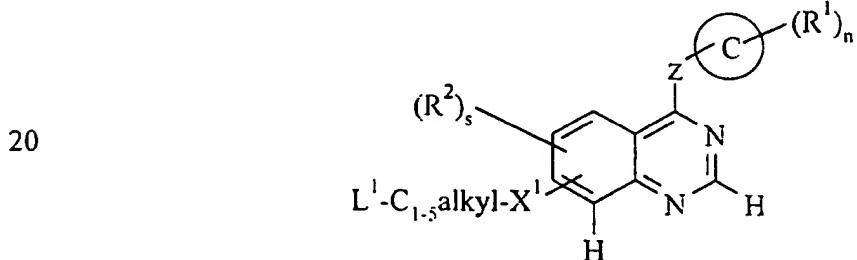
(wherein R^1 , R^2 , R^s , ring C, Z and n are as defined in claim 1 and s and L^1 are as defined herein and X^1 is as defined herein in this section);

- (d) compounds of the formula I and salts thereof wherein at least one R^2 is R^sX^1 wherein X^1 is as defined in claim 1 and R^s is $C_{1,3}$ alkylR⁶², wherein R⁶² is selected from one of the following nine groups:

- 25 1) $X^{10}C_{1,3}$ alkyl (wherein X¹⁰ represents -O-, -S-, -SO₂-, -NR⁶³CO- or -NR⁶⁴SO₂- (wherein R⁶³ and R⁶⁴ which may be the same or different are each hydrogen, $C_{1,3}$ alkyl or $C_{1,3}$ alkoxyC_{2,3}alkyl);
- 30 2) NR⁶⁵R⁶⁶ (wherein R⁶⁵ and R⁶⁶ which may be the same or different are each hydrogen, $C_{1,3}$ alkyl or $C_{1,3}$ alkoxyC_{2,3}alkyl);

- 3) $X^{11}C_{1-5}\text{alkyl}X^5R^{22}$ (wherein X^{11} represents -O-, -S-, -SO₂-, -NR⁶⁷CO-, -NR⁶⁸SO₂- or -NR⁶⁹- (wherein R⁶⁷, R⁶⁸, and R⁶⁹ which may be the same or different are each hydrogen, C₁₋₅alkyl or C₁₋₅alkoxyC₂₋₃alkyl) and X⁵ and R²² are as defined in claim 1);
- 4) R²⁸ (wherein R²⁸ is as defined in claim 1);
- 5 5) X¹²R²⁹ (wherein X¹² represents -O-, -S-, -SO₂-, -NR⁷⁰CO-, -NR⁷¹SO₂-, or -NR⁷²- (wherein R⁷⁰, R⁷¹, and R⁷² which may be the same or different are each hydrogen, C₁₋₅alkyl or C₁₋₅alkoxyC₂₋₃alkyl) and R²⁹ is as defined in claim 1);
- 6) X¹³C₁₋₅alkylR²⁹, preferably X¹³C₁₋₃alkylR²⁹, (wherein X¹³ represents -O-, -S-, -SO₂-, -NR⁷³CO-, -NR⁷⁴SO₂- or -NR⁷⁵- (wherein R⁷³, R⁷⁴ and R⁷⁵ each independently represents hydrogen, C₁₋₅alkyl or C₁₋₅alkoxyC₂₋₃alkyl) and R²⁹ is as defined in claim 1);
- 10 7) R²⁹ (wherein R²⁹ is as defined in claim 1);
- 8) X¹⁴C₁₋₅alkylR²⁸ (wherein X¹⁴ represents -O-, -S-, -SO₂-, -NR⁷⁶CO-, -NR⁷⁷SO₂- or -NR⁷⁸- (wherein R⁷⁶, R⁷⁷ and R⁷⁸ each independently represents hydrogen, C₁₋₅alkyl or C₁₋₅alkoxyC₂₋₃alkyl) and R²⁸ is as defined in claim 1); and
- 15 9) R⁵⁴C₁₋₅alkylX⁹R⁵⁵ (wherein R⁵⁴, R⁵⁵ and X⁹ are as defined in claim 1);

may be prepared by reacting a compound of the formula IX:



(IX)

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(wherein X¹, R¹, R², ring C, Z and n are as defined in claim 1 and s and L¹ are as defined herein) with a compound of the formula X:



30 (wherein R⁶² is as defined herein);

(e) compounds of the formula I and salts thereof wherein one or more of the substituents $(R^2)_m$ is represented by $-NR^{79}R^{80}$, where one (and the other is hydrogen) or both of R^{79} and R^{80} are C_{1-3} alkyl, may be prepared by the reaction of compounds of formula I wherein the substituent $(R^2)_m$ is an amino group and an alkylating agent;

5 (f) compounds of the formula I and salts thereof wherein X^1 is $-SO-$ or $-SO_2-$ may be prepared by oxidation from the corresponding compound in which X^1 is $-S-$ or $-SO-$; and when a salt of a compound of formula I is required, reaction of the compound obtained with an acid or base whereby to obtain the desired salt.

10 16. A pharmaceutical composition which comprises as active ingredient a compound of formula I or a pharmaceutically acceptable salt thereof as claimed in any one of claims 4 to 12 in association with a pharmaceutically acceptable excipient or carrier.

15 17. A method for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/03295

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D403/12 C07D401/14 C07D405/14 C07D403/14 A61K31/517

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 39145 A (RHONE-POULENC) 12 December 1996 (1996-12-12) page 1 -page 13; claims ----	1-4, 15-17
X	WO 95 15758 A (RHONE-POULENC) 15 June 1995 (1995-06-15) page 1 -page 15; claims ----	1-4, 15-17
P, X	WO 99 35132 A (GLAXO) 15 July 1999 (1999-07-15) claims -----	1,15-17



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

Special categories of cited documents:

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- "P" document published prior to the international filing date but later than the priority date claimed

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"Z" document member of the same patent family

Date of the actual completion of the international search

12 January 2000

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/03295

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